DIGITAL TECHNOLOGY IN NEUROLOGY: FROM CLINICAL ASSESSMENT TO NEUROREHABILITATION

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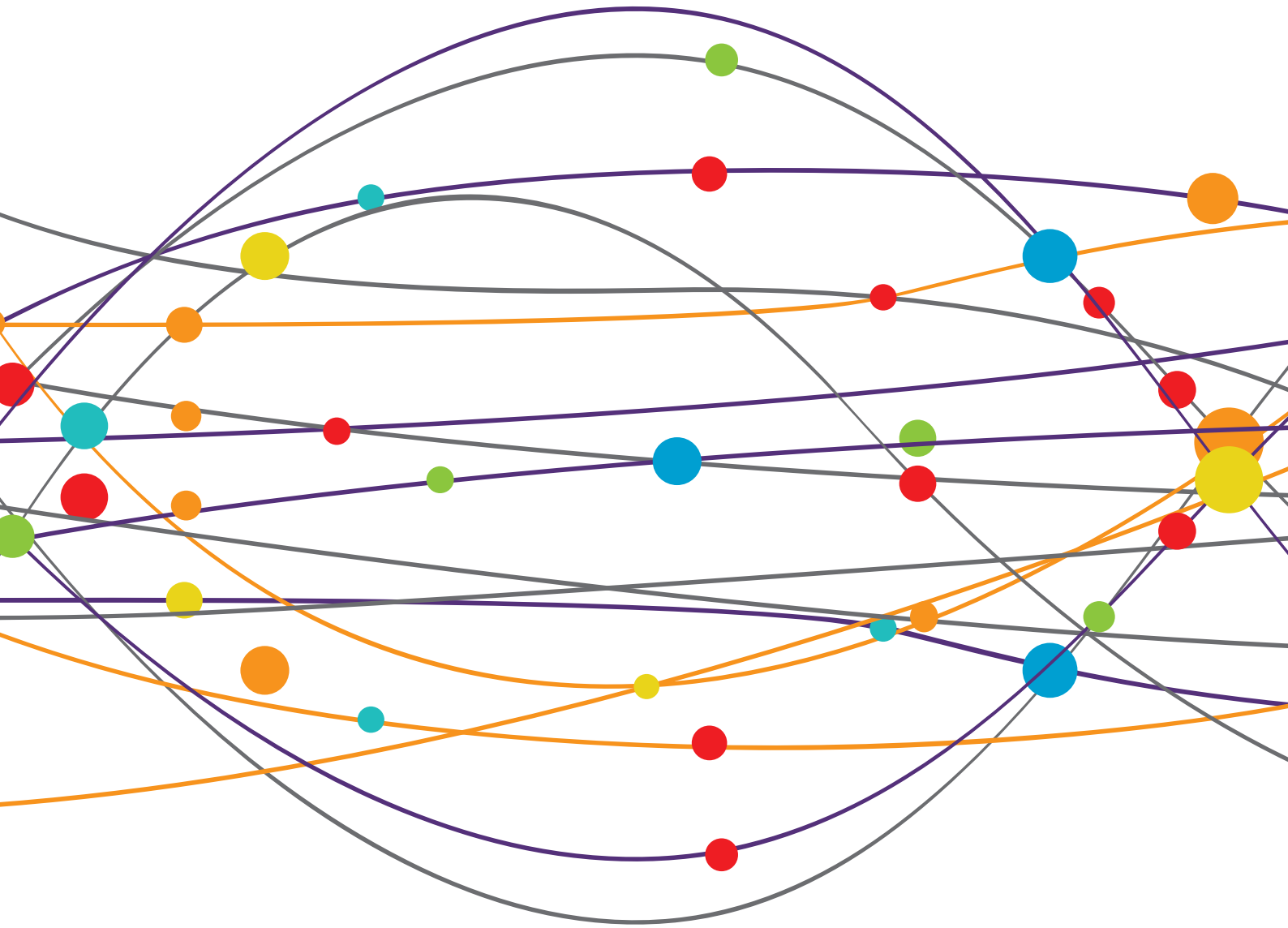
PUBLISHED IN: Frontiers in Neurology



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ISSN 1664-8714
ISBN 978-2-88966-551-8
DOI 10.3389/978-2-88966-551-8

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DIGITAL TECHNOLOGY IN NEUROLOGY: FROM CLINICAL ASSESSMENT TO NEUROREHABILITATION

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Citation: Brigo, F., Brennan, S., Moccia, M., Bonavita, S., eds. (2021). Digital Technology in Neurology: From Clinical Assessment to Neurorehabilitation. Lausanne: Frontiers Media SA. doi: 10.3389/978-2-88966-551-8

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frontiers in Neurology

EDITORIAL
published: 21 January 2021
doi: 10.3389/fneur.2020.614074

Editorial: Digital Technology in Neurology: From Clinical Assessment to Neurorehabilitation

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Keywords: digital technology, multiple sclerosis, stroke, neurorehabilitation, neurology

Editorial on the Research Topic

Digital Technology in Neurology: From Clinical Assessment to Neurorehabilitation

Over the past decades, advances in digital technology have led to the introduction of electronic health (eHealth) applications (1). Considering that many patients with chronic and disabling neurological diseases have complex healthcare needs but difficulties in access (e.g., mobility restrictions), digital technology has become progressively used to improve delivery of healthcare services, clinical assessments, and data collection in research and clinical practice. Hereby, we aim to review the results presented in this special issue on the use of digital technology in neurology (2).

Telerehabilitation encompasses prevention, evaluation, assessment, intervention, monitoring, supervision, education, consultation, and coaching, and, as such, has been used to deliver different interventions, with the possibility to provide patients with real-time feedback on rehabilitation outcomes to improve engagement and, thus, promote neuroplasticity and functional recovery. In line with this, the systematic review by Matamala-Gomez et al. has highlighted an increasing interest in creating new telerehabilitation protocols for enhancing patients' engagement by promoting self-awareness, self-management, and motivation, and by providing emotional support; of note, positive results were generally seen by enhancing the behavioral, cognitive, and emotional dimensions of patient engagement. Wu et al. have investigated the impact brain-computer interface (BCI)-based training has on upper limb rehabilitation in subacute stroke patients, using functional connectivity MRI analysis. Briefly, the BCI-based training provided users with brain state-dependent sensory feedback via functional electrical stimulation, virtual reality environments, or robotic systems, and has determined reorganization of brain functional networks topology in subacute stroke patients, with increased coordination between the multi-sensory and motor-related cortex and the extrapyramidal system. Similarly, Li et al. used repetitive transcranial magnetic stimulation (rTMS) for cognitive rehabilitation in post-stroke cognitive impairment (PSCI) and showed both cognitive improvement following rTMS, and change in neural activity and functional connectivity in cognition-related regions on resting-state functional MRI (Li et al.). Patients' satisfaction with a technology-enabled rehabilitation program was investigated by Isernia et al. in people with different central nervous system diseases, and by Høye et al. in six adults with cerebral palsy. Both studies showed the efficiency of the programs on study outcomes, and overall good feasibility (Isernia et al.; Høye et al.), suggesting that digital technology will play a crucial role in future neurorehabilitation models, with increased possibilities of customized care. Of course, there are limitations to neurorehabilitation and, for instance, Øra et al. found that internet connection issues have hindered telerehabilitation delivery in post-stroke aphasia.

OPEN ACCESS

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Specialty section:
This article was submitted to Neurorehabilitation, a section of the journal Frontiers in Neurology

Received: *05 October 2020*
Accepted: *29 December 2020*
Published: *21 January 2021*

Citation:
Moccia M, Brigo F, Brennan S and Bonavita S (2021) Editorial: Digital Technology in Neurology: From Clinical Assessment to Neurorehabilitation. Front. Neurol. 11:614074. doi: 10.3389/fneur.2020.614074

Digital technology has been used also to facilitate the remote assessment of clinical disability, patient's symptoms, adverse events, and outcomes. Sensory symptoms are generally considered difficult to evaluate, and, in an observational study, the Vibration Sensory Analyzer-3000 (VSA-3000) has shown higher diagnostic accuracy than the tuning fork in patients with impaired vibration sensation caused by central nervous system injury (stroke or spinal cord injury) (Gao et al.). Also, in another study, static post urography was able to detect subtle balance changes, and to discriminate healthy subjects from MS patients without clinically overt disability, thus suggesting this could be used to complement neurological examination for a more sensitive and objective assessment of balance and subsequent risk of falls (Inojosa et al.).

Advances in digital health and information technology have allowed collecting clinical data in a standardized and quantitative way, facilitating both research and patient care, especially in the MS field. For instance, the "Integrated Care Portal MS" is a portal for MS patients and health care professionals encompassing a pathway-based care model to better diagnose, monitor long-term, and thus optimally treat individual MS patients (Voigt et al.). Similarly, the "MS Documentation System" enabled the collection of clinical data into an eHealth platform (Ziemssen et al.), and the "MS Partners Advancing Technology and Health Solutions" allowed standardized data collection across 10 healthcare institutions (Mowry et al.). Moreover, Allen-Philbey et al. showed the potential of collecting data by combining clinical assessments and patient-reported outcomes, using a platform shared between a large data repository, the UK MS Register at Swansea University, and BartsMS in east London, UK. As such, authors have facilitated databases for research, service audit, and individual patient care, and have specifically highlighted the important role of public and patient involvement throughout the design and implementation process (Allen-Philbey et al.).

Shortcomings of digital technology could include its feasibility in the neurology field. However, Lavorgna et al. have investigated the attitude of neurologists toward the use of the internet, and showed a broad use of digital devices in clinical practice, with more than half participants using social media for communicating with patients, suggesting this is prime time for digital technology in neurology clinical practice.

In conclusion, this Research Topic has shown current applications of digital technology in neurology, from clinical assessment to data collection and rehabilitation. Results hereby presented have further gained relevance over the recent months, in light of the COVID-19 pandemic with many consultations and clinical assessments being now delivered remotely (3). In the future, based on these findings, we will be able to improve individualized care in neurological diseases, while keeping patients fully engaged in their management plan.

AUTHOR CONTRIBUTIONS

MM and FB: literature search and drafting the manuscript. SBr and SBo: literature search and revising the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

CLINICAL TRIAL
published: 19 November 2019
doi: 10.3389/fneur.2019.01206

Efficiency and Patient-Reported Outcome Measures From Clinic to Home: The Human Empowerment Aging and Disability Program for Digital-Health Rehabilitation

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Specialty section:
This article was submitted to Neurorehabilitation, a section of the journal Frontiers in Neurology

Received: *06 August 2019*
Accepted: *29 October 2019*
Published: *19 November 2019*

Citation:
Isernia S, Pagliari C, Jonsdottir J, Castiglioni C, Gindri P, Gramigna C, Palumbo G, Salza M, Molteni F and Baglio F (2019) Efficiency and Patient-Reported Outcome Measures From Clinic to Home: The Human Empowerment Aging and Disability Program for Digital-Health Rehabilitation. Front. Neurol. 10:1206. doi: 10.3389/fneur.2019.01206

Background: The recent exponential growth of Digital Health (DH) in the healthcare system provides a crucial transformation in healthcare, answering to alarming threats related to the increasing number of Chronic Neurological Diseases (CNDs). New long-term integrated DH-care approaches, including rehabilitation, are warranted to address these concerns.

Methods: The Human Empowerment Aging and Disability (HEAD) rehabilitation program, a new long-term integrated care including DH-care system, was evaluated in terms of efficiency and patient-reported outcome measures (PROMs) in 107 CND patients (30 with Parkinson's Disease, PD; 32 with Multiple Sclerosis, MS; 45 with stroke in chronic stage). All participants followed 1-month of HEAD rehabilitation in clinic (ClinicHEAD: 12 sessions, 3/week), then 1:3 patient was consecutively allocated to 3-months telerehabilitation at home (HomeHEAD: 60 sessions, 5/week). Efficiency (i.e., adherence, usability, and acceptability) and PROMs (i.e., perceived functioning in real-world) were analyzed.

Results: The rate of adherence to HEAD treatment in clinic ($\geq$90%) and at home (77%) was high. Usability of HEAD system was judged as good (System Usability Scale, median 70.00) in clinic and even more at home (median 80.00). Similarly, administering the Technology Acceptance Model 3 questionnaire we found high scores both in clinic/at home (Usefulness, mean 5.39 $\pm$ 1.41 SD/mean 5.33 $\pm$ 1.29 SD; Ease of use, mean 5.55 $\pm$ 1.05 SD/ mean 5.45 $\pm$ 1.17 SD, External Control, mean 4.94 $\pm$ 1.17 SD/mean 5.07 $\pm$ 1.01 SD, Relevance, mean 5.68 $\pm$ 1.29 SD/mean 5.70 $\pm$ 1.13 SD and Enjoyment, mean 5.70 $\pm$ 1.40 SD/mean 6.01 $\pm$ 1.08 SD). After ClinicHEAD, participation and autonomy in daily routine was maintained or even ameliorated (PD and stroke > MS). Whereas, increased functionality and participation in the MS group was found only after HomeHEAD intervention.

Discussion: Our results suggest that a tele-health-based approach is both feasible and efficient in providing rehabilitation care to CNDs from clinic to home. Increasing and maintaining participation as well as autonomy in daily routine are promising findings that open up scenarios for the continuity of care at home through DH-care for CNDs.

Keywords: rehabilitation, technology, telerehabilitation, nervous system diseases, multiple sclerosis, Parkinson's disease, stroke

INTRODUCTION

Parkinson Disease (PD), Multiple Sclerosis (MS), and Stroke are the more frequent chronic Neurological Diseases (CNDs) that can lead to significant motor and cognitive disability: worldwide data report 2.5 million people with MS (1), 7.9 to 19 individuals with PD per 100,000 person-year (2) and 5.5 million deaths due to stroke in 2016 (3). In recent years, new models of digital health (DH) enabling continuity of care are increasingly explored as new solutions to the long-term patient maintenance. Also, growing effort has been spent in the development of technology-enabled treatments, able to be carried out outside clinic setting, with promising results (4–14). Especially, telerehabilitation aids in decreasing socioeconomic costs related to these pathologies and their weight on the healthcare system (15–17). Also, technology-enabled rehabilitation at home allows people with chronic diseases to combine pathology management with their everyday social life (5).

To ensure effectiveness of tele-treatment, a continuous double loop communication between home and clinic environment is needed: in this sense, digital health care platforms constitute the central hub through which health professionals can monitor patient performance at home (18) and consequently modify treatment during the whole period of telerehabilitation. Frequency of rehabilitation and duration of treatment are important parameters that should not be overlooked. In fact, there are health care guidelines for clinical practitioners that detail the frequency and duration of rehabilitation activities specifically for different pathologies, such as MS, PD and stroke (19). For example, strength training, reported as efficacious for MS, PD and stroke patients (20–22) should be performed 2–3 days per week to reach benefits on daily living with a duration per session ranging between 10 and 40 minutes. However, little is known regarding frequency and dose treatment guidelines for treatments administered in a home-based setting.

Unfortunately, adherence to home rehabilitation protocols, including telerehabilitation, is a concern (23). People with neurological disorders that could benefit from rehabilitation often do not adhere to a prescribed protocol once they are in their home environment. This could provide serious consequences, such as loss of functioning, pain, muscle wasting etc., that are risks deriving from a lack of rehabilitation not only in an acute condition, but also in a chronic phase. Few recent studies have investigated the factors affecting adherence in order to predict and enhance adherence to telerehabilitation. An interesting work created a quantitative adherence prediction model based on baseline patients' characteristics by individualizing an important predictive role of education, satisfaction about the treatment and psychological profile (24). Another contribution investigated variation of adherence to treatment comparing different modes of cycling treatment administration, such as active or passive exercises, reporting more satisfying adherence to the passive mode of exercises (25). These contributions demonstrated a pivotal interest on the topic.

Another aspect to be considered regarding new DH approaches is the active role of the patient that is empowered and engaged in own care management, with consequences also on perceived care outcome. In particular, an "e-patients" term has been coined to highlight patients involved in decision-making and management of their own care (26). In fact, patient-reported outcome measures (PROMs) are increasingly used as real-world functioning measures that incorporate self-defined assessments of personal well-being during the management of care (27). Recent clinical practice health guidelines promote the integration of these latter measures into long-term care of patients (28).

The present study aims to report results on efficiency measures and PROMs of the Human Empowerment Aging and Disability program (HEAD), a DH-telerehabilitation system for people with chronic neurological diseases. In particular, we tested HEAD treatment during 1-month of rehabilitation program in clinic and during 3-months of HEAD telerehabilitation at home, comparing patients performances for PD, MS, and chronic stroke.

MATERIALS AND METHODS

Participants

The study was carried out in two steps: ClinicHEAD and HomeHEAD. In the ClinicHEAD (first step) subjects with PD, MS, and chronic stroke ($N = 107$) were consecutively recruited. They were identified by the neurologists of the clinics from people that periodically receive neurological follow-up (outpatients) from the respective centers: Valduce Hospital Villa Beretta Rehabilitation Center in Lecco ($n = 34$; 17 stroke, 7 PD, 10 MS), IRCCS Don Carlo Gnocchi Foundation in Milan ($n = 43$, 12 stroke, 10 PD, 21 MS) and District Clinic San Camillo in Turin ($n = 30$, 16 stroke, 13 PD, 1 MS).

Inclusion criteria for enrollment were: [a] age range 18–80; [b] diagnosis of PD in stable treatment for at least 3 years and with a Hoehn and Yahr score ≤ 2 (29), diagnosis of MS without relapses in the last 3-months and with an Expanded Disability Status Scale [EDSS (30)] score ≤ 5.5, diagnosis of stroke in chronic phase, at least 6-months after the acute event.

Exclusion criteria for recruitment were the following: [a] Mini Mental State Examination (31) score < 20; [b] presence

of disabling pain; [c] upper limb limited passive range of motion; [d] epilepsy; [e] severe deficit of visual acuity and auditory perception; [f] severe deficit in communication and severe dysmetry.

After enrollment and baseline assessment, they were consecutively assigned into the Clinic and Home HEAD programs.

All participants provided written and informed consent to take part in the study.

The HEAD Program

The HEAD rehabilitation was conceived as a multidimensional program for the continuity of care at home for patients with chronic neurological diseases. It aimed to enhance motor and cognitive abilities such as balance, lower and upper body endurance, strength and speed, memory, executive functions, language and dual-tasking activities, in order to improve patient's everyday functional skills. Procedure and contents of each rehabilitative activity was defined by a health professionals' team including neurologists, physiotherapists and neuropsychologists. **Table 1** describes all activities included in HEAD rehabilitation program.

The HEAD virtual platform represented the hub for communication between the clinic and the patient's home, allowing rehabilitation activities to be administered through a gaming setting in order to work on goal-directed movements in a virtual reality (VR) scenario. This platform was designed as a bridge between clinic and patient's home setting, making a double loop feedback possible between the two environments. Before every rehabilitation session, physiotherapists and psychologists defined the contents of the session, in the sense of type of activities, repetitions and level of difficulty through the HEAD virtual platform. In this manner, although HEAD technology allowed the same setting for each patient, contents of the rehabilitation program were tailored and personalized according to the different needs related to the pathology of the patient and the level of disability. Patients accessed the platform with their own credentials to start each telerehabilitation session and, health professionals were able to tailor rehabilitation along the whole period of treatment by remotely checking the quality of the gaming performance of the patient reported in the platform.

To run the HEAD program, a PC, internet connection and motor capture devices, such as Kinect (Microsoft, WA, USA) and Leap Motion (Leap Motion Inc., CA, USA), were needed.

The rehabilitation activity was embedded in short video clips. Each video clip lasted from 2 to 9 minutes, and was interrupted between 2 to 6 times on the basis of repetitions of the rehabilitation activity. In general, video clips had three main purposes: as motivating breaks that inter-cut the rehabilitative activities, providing emotional and cognitive stimuli regarding the rehabilitative activities, or awarding the participant at the end of the exercise. Many of the motor and cognitive exercises were directly related to the video. Thus, participants had to erase an image just seen, by means of large movements of the arms in order to continue watching the clip. Alternatively, participants were asked to order the sequences of the film clip just seen, or had to answer questions about the content of the film clip. Patients thus actively controlled their viewing of the movie clips and their progression.

Each activity ended with a feedback of the results, according to an algorithm based on the percentage of completion, number of errors and duration of the performance. The scoring was illustrated by stars, with a minimum of 1 to a maximum of 5 stars being awarded.

During the month of treatment in clinic, the HEAD program was supervised by physiotherapists and neuropsychologists and was administered through 45 min sessions 3 times per week. Once at home, the HEAD program was carried out five consecutive days per week, 30–45 min each session.

Each participant accessed the HEAD portal through his personal credentials to perform his own individual daily program consisting of 3–6 neuromotor activities according to his needs. The participants were free to choose the time of day and weekdays in which to carry out the activities. Finally, participants had the opportunity of calling the Help Desk Service or therapists for technical problems or related issues. A phone call by therapists to participants was planned once a week to check for patient compliance.

Measures

All patients recruited were administered a rehabilitation with VR technology for 1-month in clinic (Time 1: ClinicHEAD). After rehabilitation in clinic, patients were consecutively allocated to HEAD telerehabilitation at home for 3-months (Time 2: HomeHEAD) with a ratio of 1:3. This ratio was due to the limited availability of the HEAD technological kits. For this reason, one patient each three was allocated to continue treatment for 3-months at home. In the second step of the study the participants not allocated to the HomeHEAD group were asked to not participate in physical activities different from those that they would usually do during the protocol duration (control group). Subsequent contributions will report efficacy of HEAD treatment based on outcome measures in each CND included in the study.

Efficiency and Patient-Reported Outcome measures were collected after ClinicHEAD rehabilitation (Time 1) and after 3-months of HomeHEAD treatment by clinicians blind to the treatment allocation (Time 2).

Part of data were obtained through questionnaires administered by a psychologist, while remaining data were extracted from the HEAD platform.

The present work, registered as Clinical Trial ID: NCT03025126, provides preliminary data on efficiency of the HEAD protocol.

Baseline Assessment

Patients recruited were screened with:

(1) Montreal Cognitive Assessment [MoCA (32)] as a measure of global cognitive functioning. Conti's correction was adopted to transform scores on the basis of age and years of education of people. This tool allowed a brief screening of cognitive level evaluating different domains:

TABLE 1 | List and brief description of HEAD activities.

Activities	Description
UPPER LIMBS WARMING-OUT	
"Delete and Go"	*Movie stops and subject has to perform movements of arms detected by Kinect or Leap Motion Controller (LMC) in order to delete the movie screenshot that appears in the screen. When the 80% of the screenshot has been deleted the movie continues*
"Unveil and Go"	*Movie stops and subject has to perform movements of arms detected by Kinect or LMC in order to unveil the screenshot of the movie that appears covered on the screen. When the 80% of the screenshot has been unveiled the movie continues*
"Swim and Go"	*Movie stops and subject is required to perform a certain numbers of strokes detected by Kinect or LMC to continue the vision of the movie*
LOWER LIMBS WARMING-OUT	
"Up and Go"	*Movie stops and subject is asked to perform up-the-stairs movements detected by Kinect to climb virtual stairs in order to reach the movie screenshot that appears at the end of the stairs and let video continue*
"Goal and Go"	*Movie stops and subject has to perform a hit-the-ball movement detected by Kinect: each correct movement corresponds to a percentage of zooming of the screenshot of the movie. The maximum zoom of the screenshot let movie continue*
UPPER LIMBS PRECISE MOVEMENT	
"Turn pages and watch"	*Movie stops and a book with figures related to the video appears. Subject has to perform turn-pages movements detected by LMC to let movie continue*
"Grasp and Move"	*Movie stops and different images presented in the video appear on the screen. Subject has to grasp and move them in a box through hand movement detected by Kinect or LMC to let video continue*
"Pinch and Take"	*Movie stops and different images presented in the video appear on the screen. Subject has to grasp and move them in a box through pinch movement detected by LMC to let video continue*
LOWER LIMBS PRECISE MOVEMENT	
"Dribble and watch"	*Movie stops and subject has to juggle a ball by performing dribble-ball movements detected by Kinect sensor to let video continue*
"March and Go"	*Movie stops and subject has to perform march movements detected by Kinect in order to get nearer the screenshot of the movie, that appears far, to let video continue*
TORSO MOVEMENT	
"Play and watch"	*Movie stops and subject has to play drums by managing the movement of the chopstick through torso movements detected by Kinect to let video continue*
EXECUTIVE FUNCTION	
"Maze"	*After watching video, subject has to perform harm and torso movements detected by Kinect to guide a ball in a maze in order to reach the exit which reports the right category of the video*
"Shaky Trunk"	*After watching video, several words, both related to the movie and not related, appear on the screen. Subject has to select only the words related to the video by a grasp movement of the hand detected by Kinect. Then, different trunks on which is placed a ball appear. Subject has to manage the direction of the ball through torso movements detected by Kinect in order to let the ball fall in the box of the same color*
"Puzzle"	*Movie stops and subject has to complete a puzzle depicting a screenshot of the movie*
MEMORY	
"In the box"	*After watching video, subject is required to perform torso or hand movements detected by Kinect in order to manage the direction of a box while images related and not related to the movie fall up to down. Subject has to catch only images related to the movie*
"Reorder and win"	*After watching video, subject has to order a set of screenshots following the sequential order of video events through arm movements detected by LMC*
LANGUAGE	
"Quiz: grasp the answer"	*After watching video, subject has to solve a quiz by choosing the right answer regarding video content through hand movements detected by LMC*
LEISURE ACTIVITIES	
"Shaving"/ "Making-up"/"Shampooing"	*Subject has to reorder actions required for shaving/making-up/shampooing in sequence. Then, different objects appear on the screen and subject is required to grasp a certain object related with this activity. Finally, a photo of a man appears on the screen and subject has to imitate movements related to shaving/making-up /shampooing on the image by hand movements detected by LMC. After activity, movie start as a reward*
DUAL TASK	
"Pair symbols with similarity"	*Different images appear on the screen. Subject has to pair equal images with ratio 1:1 or 1:2 or 1:3 and move them in a box by paying attention to do not touch different images through hand movements detected by LMC. After activity, movie start as a reward*
"Pair number and object"	*Subject has to memorize an association between number and object and then pair the right number with the right object through hand movements detected by LMC. After activity, movie start as a reward*

attention, executive functions, memory, language, visual-spatial abilities, abstraction, calculation, and orientation. Score range is 0–30, with a maximum score of 30.

(2) 2 Minute Walk Test [2MWT (33)] for a quantitative analysis of gait endurance. Participants were instructed to walk as far as possible over 2 minutes and the distance covered was collected.

(3) 10 Meter Walk Test [10MWT (34)] to measure gait speed. Participants were required to walk 10 meters while time was measured. The score was obtained by dividing the distance by the time spent to cover it.

Output Measures

System Usability Scale [Brooke (35)] was administered for a measure of perceived easiness of use of the HEAD system. This is a 10-item, 5 point Likert scale (1= strongly disagree, 5= strongly agree). Scoring instructions of Brooke (35) were considered. The final score ranges from 10 to 100. A cut-off score, indicating a satisfying level technological system's usability, is 68. Learnability and usability sub-scores were also obtained in accordance to Lewis and Sauro's indications (36, 37).

Adherence to treatment in clinic and at home was calculated by extracting the following indexes from output of the platform: percentage of total sessions performed, mean number of activities performed per session, mean duration of activities performed per session. We analyzed the same indexes singularly per each week of telerehabilitation at home. Additionally, we analyzed the number of sessions per week performed considering 3 session/week as the recommended frequency of rehabilitation, following Kim's et al. (19) indications. We considered as drop-out participants who followed <50% of treatment period in clinic (<2 weeks of treatment) and at home (<6 weeks of treatment).

Technology Acceptance Model-3 (38) was utilized in order to deepen patients' beliefs related to their inclination to experience the HEAD system. This scale, in fact, specifically explores the perceived ease of use, such as the degree of difficulty that the use of a technology system involves, and the perceived usefulness, as the belief that the use of a specific technology system allows improving one's own productivity. For the purpose of the present study, we focus our analysis only on determined domains of the scale: Perceived usefulness, perceived ease of use, perceptions of external control, perceived enjoyment, Job relevance. Response on a 7-point Likert scale were collected (Totally Disagree = 1/ Totally Agree = 7).

Finally, an *ad-hoc* questionnaire was created with the purpose to investigate specific barriers patients experienced during rehabilitation at home. This tool was additionally administered to patients recruited in Don Gnocchi Foundation for a deepened investigation. The questionnaire was composed by 11 items with a 5-point Likert scale (0 = Absolutely not/Never, 4 = Very much/Always) (see **Table S1** to consult the tool). The questionnaire was scored grouping items into 5 groups in order to obtain 5 total indexes related to crucial aspects to investigate barriers encountered during experience of telerehabilitation. In particular, we analyzed answers extracting the following indexes: (1) motivation (mean score of item 6 and 8) [*Did you need support of other persons (ex. your son, bride/wife…) to be motivated to perform HEAD activities (did they remind you to do them?)/ When I didn't perform activities it was because I wouldn't*], (2) logistics (mean score of item 1 and 2) [*Did having HEAD system at home bother you?"*/"*How much did you need to modify arrangement of furniture to place HEAD technology devices?*"], (3) autonomy (mean score of item 5 and 6) [*Did you need support of other persons (ex. Your son, bride/wife…) to prepare HEAD technology setting?/ Did you need support of other persons (ex. your son, bride/wife…) to perform HEAD activities?*], (4) inclusion in the routine (mean score of item 3, 4 and 9) [*Did you modify your routine to include HEAD activities during the week (ex. Did you eat earlier than usual? Did you stop to have nap after lunch?)/Did you renounce to perform other activities to do HEAD program?/ When I didn't perform activities it was because I couldn't*], (5) technical problems (mean score of item 10 and 11) [*When I didn't perform activities it was because the system did not work/When I didn't perform activities it was because even if the system worked, the internet connection did not*].

Patient-Reported Outcome Measures

Two categories of International Classification of functioning [ICF (39)] on activities and participation in daily life were considered as PROMs: Carrying out daily routine (d230) and Recreation and leisure (d920). These categories were extracted by administering the item 3 of EuroQoL EQ-5D-5L (40–43) and the item 12 of Short Form 12 health survey questionnaire [SF12 (44–47)], respectively. These two items were then translated in the 5 ICF qualifiers. Specifically, we associated ICF qualifier 4 (complete problem) to answer "All the time/Extremely," qualifier 3 (severe-complete problem) to answer "Most of the time/a good bit of the time/Quite bit," qualifier 2 (moderate-severe problem) to answer "Some of the time/Moderately," qualifier 1 (mild-moderate problem) to answer "A little of the time/a little bit" and qualifier 0 (no problem) to answer "Never/Not," following previous mapping works (44, 46).

Statistical Analysis

Statistical analysis was performed using MedCalc® Software Version 15.2.1.

Normal distribution of variables was checked through Kolmogorov-Smirnov normality test. According to this test, parametric or non-parametric analysis were performed for the comparison among three pathology groups (PD vs. MS vs. stroke).

To analyze efficiency measures such as adherence to HEAD treatment, usability and acceptance of the HEAD system, descriptive statistics were run in each pathology group. Comparison among groups was also reported through ANCOVA or General Linear Model, by covarying for recruitment center. Bonferroni *post-hoc* test was considered. To analyze *ad-hoc* questionnaire results we performed descriptive statistics.

To analyze PROMs, we reported the distribution of qualifiers (percentages) of the ICF categories at the different time points (Enrollment T0, post ClinicHEAD T1, and post HomeHEAD

TABLE 2 | Summary statistics and comparison results of patient groups at baseline.

	PD	MS	Stroke	Comparison [Test (*p*)]	All
TIME 1: ClinicHEAD					
N	30	32	45	–	107
Age (M ± sd)	66.30 ± 8.77	52.75 ± 10.62	61.04 ± 13.25	11.29 (<0.001)	60.04 ± 12.43
Sex (M:F)	16:14	15:17	26:19	0.89 (0.640)	57:50
Education	11.73 ± 4.40	11.22 ± 3.25	12.44 ± 4.12	0.92 (0.401)	11.88 ± 3.96
MoCA	23.60 ± 3.41	23.69 ± 3.19	21.71 ± 4.79	3.05 (0.051)	22.83 ± 4.08
2MWT	131.66 ± 37.30	92.36 ± 34.11	81.94 ± 43.91	13.72 (<0.001)	100.77 ± 44.44
10MWT	1.41 ± 0.52	0.98 ± 0.52	0.84 ± 0.47	10.55 (<0.001)	1.07 ± 0.55
TIME 2: HomeHEAD					
N	11	14	13	–	38
Age (M ± sd)	65.55 ± 9.06	51.93 ± 8.76	57.77 ± 17.17	3.73 (0.034)	57.87 ± 13.25
Sex(M:F)	4:7	7:7	6:7	0.48 (0.112)	17:21
Education	11.27 ± 4.69	12.07 ± 3.25	14.85 ± 4.00	2.79 (0.075)	12.79 ± 4.15
MoCA	22.91 ± 3.21	23.85 ± 3.74	22.62 ± 5.44	0.20 (0.819)	23.13 ± 4.20
2MWT	131.64 ± 38.94	93.96 ± 31.57	79.54 ± 26.22	7.31 (0.003)	101.27 ± 38.36
10MWT	1.43 ± 0.59	1.04 ± 0.47	0.83 ± 0.34	4.48 (0.019)	1.09 ± 0.52

2MWT, 2 minutes walk test; 10MWT, 10 meters walk test; M, mean; MoCA, Montreal Cognitive Assessment; MS, multiple sclerosis; N, number; PD, Parkinson Disease; sd, standard deviation.

T2). Then, patients were classified into delta score ≤ 0, indicating a perception of maintenance or amelioration over time, and delta score > 0, referring a perception of worsening over time. Percentages of sample reporting delta score ≤ 0, reported as stable/ameliorated patients, and delta score > 0, as worsened patients, were calculated and Chi-square χ^2 was performed. Results were considered statistically significant when $p < 0.05$.

RESULTS

Participants

Table 2 shows demographic characteristics of sample included in the study.

ClinicHEAD: All patients enrolled in the study ($n = 107$) followed a program of 12 sessions of HEAD rehabilitation in clinic. A total of 107 patients with CNDs was composed of 30 people with PD, 32 with MS and 45 with chronic stroke. The three groups were comparable in terms of gender distribution ($\chi^2 = 0.89$, $p = 0.640$) and years of education ($F = 0.92$, $p = 0.401$) while there was a statistically significant difference in age between MS and the other two groups ($F = 11.29$, $p < 0.001$). In terms of global cognitive level, we found a trend for a lower MoCA score in stroke patients compared to those with MS or PD ($F = 3.05$, $p = 0.051$). Finally, endurance and velocity assessed through 2MWT and 10MWT scores were significantly higher in PD than in other patients' groups (2MWT: $F = 13.72$, $p < 0.001$; 10MWT: $F = 10.55$, $p < 0.001$).

HomeHEAD: Thirty-eight patients were then allocated to HomeHEAD treatment after ClinicHEAD period to test the system for the continuity of care at home. In particular, 11 PD, 14 MS, 13 stroke were assigned to telerehabilitation at home. Similarly to the ClinicHEAD sample, patients groups were comparable for gender distribution ($\chi^2 = 0.479$, $p = 0.112$) and education ($F = 2.79$, $p = 0.075$), but not for age: we reported a statistically significant difference between PD and MS group ($F = 3.73$, $p = 0.034$). The three groups did not differ in MoCA score. Instead, endurance assessed through 2MWT was significant higher in PD than in other patients' groups ($F = 7.31$, $p = 0.003$) and velocity assessed through 10MWT was major in PD than stroke ($F = 4.48$, $p = 0.019$).

The group enrolled for *ClinicHEAD* and the sub-group allocated to *HomeHEAD* did not significantly differ in gender distribution ($\chi^2 = 1.42$, $p = 0.116$), age ($F = 2.00$, $p = 0.160$), education ($F = 2.33$, $p = 0.130$), global cognitive level ($F = 0.15$, $p = 0.698$), endurance ($F = 0.03$, $p = 0.868$), and velocity ($F = 0.33$, $p = 0.569$).

Efficiency Measures Results

In **Table 3** we report data on efficiency measures after ClinicHEAD (Time 1) and after HomeHEAD (Time 2), in the three pathologies.

After ClinicHEAD we found a high level of adherence to treatment in all three patients' groups (mean score of all sample: 0.92 ± 0.13) with no significant differences among patients' groups ($F = 1.23$, $p = 0.296$). In terms of duration of treatment, as number of activities per session and minutes per session, each session consisted of about 40 minutes multidimensional treatment and was composed of about 4–5 activities. We did not find differences among groups in number of activities ($F = 0.40$, $p = 0.675$) and minutes of session ($F = 0.90$, $p = 0.408$). We registered only 1 drop out. In terms of perceived usability of the HEAD system in clinic, we reported a good level of usability, with a median SUS score of 70.00 in all patients' groups with no differences among pathologies ($F = 0.77$, $p = 0.679$). Finally, considering sub-domains of TAM3, such as perceived system Usefulness, Ease of use, External control,

TABLE 3 | Efficiency measures results of treatment in clinic.

	PD	MS	Stroke	Comparison [Test(*p*)]	All
TIME 1: ClinicHEAD					
N	30	32	45	–	107
Adherence	0.93 ± 0.11	0.90 ± 0.18	0.94 ± 0.10	1.23(0.296)*	0.92 ± 0.13
Duration of treatment (M ± sd)					
Number of activities	4.54 ± 1.70	4.97 ± 1.39	4.16 ± 0.88	0.90(0.408)*	4.51 ± 1.34
Duration of session, min	39.62 ± 18.14	43.70 ± 18.54	36.81 ± 13.05	0.40(0.675)*	39.65 ± 16.42
SUS (Median, 25–75 percentile)	68.75, 60.00–82.50	75.00, 62.50–84.38	70.00, 62.50–80.63	0.77 (0.679)§	70.00, 62.50–82.50
Usability	2.88, 2.63–3.29	3.14, 2.75–3.43	3.00, 2.63–3.38	1.64 (0.440)§	3.00, 2.63–3.43
Learnability	3.00, 1.50–3.50	2.50, 1.50–3.50	2.50, 1.50–3.50	0.99 (0.605)§	2.50, 1.50–3.50
TAM3 (M ± sd)					
Usefulness	5.54 ± 1.36	5.08 ± 1.58	5.50 ± 1.31	2.82(0.065)*	5.39 ± 1.41
Ease of use	5.59 ± 0.92	5.53 ± 1.09	5.55 ± 1.12	0.28(0.760)*	5.55 ± 1.05
External control	5.05 ± 0.92	4.93 ± 1.39	4.86 ± 1.15	0.77(0.466)*	4.94 ± 1.17
Relevance	5.84 ± 1.51	5.30 ± 1.40	5.84 ± 0.99	1.37(0.260)*	5.68 ± 1.29
Enjoyment	5.67 ± 1.33	5.91 ± 1.02	5.56 ± 1.66	0.47(0.629)*	5.70 ± 1.40
TIME 2: HomeHEAD					
N	11	14	13	–	38
Adherence	0.86 ± 0.14	0.66 ± 0.28	0.82 ± 0.15	6.00(0.007)*	0.77 ± 0.22
Duration of treatment (M ± sd)					
Number of activities	3.88 ± 0.90	4.03 ± 0.83	3.24 ± 0.42	0.81 (0.457)*	3.72 ± 0.80
Duration of session, min	37.74 ± 7.61	37.57 ± 9.89	30.66 ± 5.67	0.72 (0.497)*	35.17 ± 8.47
SUS (Median, 25–75 percentile)	85.00, 77.50–92.50	67.50, 55.00–85.00	80.00, 68.13–84.38	3.14 (0.205)*	80.00, 67.50–85.00
Usability	3.36, 3.25–3.71	2.86, 2.42–3.43	3.13, 2.65–3.50	2.46 (0.292)*	3.20, 2.57–3.50
Learnability	4.00, 2.50–4.00	2.50, 1.50–3.63	3.00, 2.63–3.88	3.06 (0.195)*	3.00, 2.00–4.00
TAM3 (M ± sd)					
Usefulness	5.25 ± 1.97	5.23 ± 1.11	5.53 ± 0.10	1.47(0.254)*	5.33 ± 1.29
Ease of use	4.68 ± 1.10	5.75 ± 1.21	5.65 ± 1.01	2.18(0.139)*	5.45 ± 1.17
External control	4.89 ± 0.45	4.95 ± 1.27	5.38 ± 0.95	0.50(0.613)*	5.07 ± 1.01
Relevance	5.62 ± 1.50	5.50 ± 1.10	6.04 ± 0.90	0.50(0.616)*	5.70 ± 1.13
Enjoyment	6.00 ± 1.29	5.97 ± 0.10	6.06 ± 1.14	0.97 (0.396)*	6.01 ± 1.08

*M, mean; MS, multiple sclerosis; N, number; PD, Parkinson Disease; sd, standard deviation; SUS, System Usability Scale; TAM3, Technology Acceptance Model-3. *ANCOVA comparison was performed co-varying recruiting center, age, gender, education; §Kruskall-Wallis test was performed.*

Relevance and Enjoyment, data of all groups supported the high level of functionality of HEAD technology (Usefulness: mean score 5.39 ± 1.41; Ease of Use: mean score 5.55 ± 1.05; External Control: mean score 4.94 ± 1.17), the perceived treatment efficacy (Relevance: mean score 5.68 ± 1.29) and the motivating aspects of HEAD contents (Enjoyment: mean score 5.70 ± 1.40). No differences among patients' groups were registered in all TAM3 subscores (Usefulness: $F = 2.82$, $p = 0.065$; Ease of Use: $F = 0.28$, $p = 0.760$; External control: $F = 0.77$, $p = 0.466$; Relevance: $F = 1.37$, $p = 0.260$; Enjoyment: $F = 0.47$, $p = 0.629$).

At HomeHEAD (Time 2), we registered 7.89% of drops in the whole group. In general, we reported a discrete adherence to treatment at home (mean score in whole group: 0.77 ± 0.22). More specifically, we observed a better adherence to treatment in PD and stroke groups than in the MS group ($F = 6.00$, $p = 0.007$). Focusing on duration of treatment, we did not find group differences in the number of activities performed per session ($F = 0.81$, $p = 0.457$) nor in the length of treatment per session ($F = 0.72$, $p = 0.497$).

Patient assessment of system usability, as shown by SUS score, was higher in the PD group (median: 85.00) compared to stroke (median: 80.00) and MS (median: 67.50) groups. In general, usability of the system at home was estimated as good (median of whole group: 80.00). No differences among pathologies groups were reported ($F = 3.14$, $p = 0.205$).

Results of TAM3 questionnaire highlighted high level of functionality of the system at home in all domains explored (Usefulness: 5.33 ± 1.29; Ease of Use: 5.45 ± 1.17; External

Control: 5.07 ± 1.01; Relevance: 5.70 ± 1.13; Enjoyment: 6.01 ± 1.08), suggesting that patients perceived HEAD program as useful, easy to use, intuitive, relevant for everyday life and playful. Again, patients' groups did not differ in TAM3 subscores (Usefulness: $F = 1.47$, $p = 0.254$; Ease of Use: $F = 2.18$, $p = 0.139$; External Control: $F = 0.50$, $p = 0.613$; Relevance: $F = 0.50$, $p = 0.616$; Enjoyment: $F = 0.97$, $p = 0.396$).

Additionally, adherence to single sessions at home for all period of telerehabilitation (60 sessions, 5 sessions/week) was observed. In particular, we analyzed adherence to sessions in each single week of treatment in each pathology group, considering percentage of adherence to session in each week (1 = adherence to 5 sessions/week; 0 = adherence to 0 sessions/week).

Table 4 reports percentage of adherence to sessions in each week (1 = adherence to 5 sessions/week; 0 = adherence to 0 sessions/week) and the mean number of activities per session in each of 12 weeks of treatment at home.

Based on recent data on recommended frequency of treatment to guarantee rehabilitation effectiveness (19), we considered 0.60 as the ideal adherence per week (3 sessions/5 per week = 1.00). We reported a good adherence (more than 88%) of PD group from the second to the eleventh week of treatment. Stroke group showed an adherence > 80% from the first to the eighth week of treatment, followed by a discrete adherence (75%) in the ninth and tenth week. MS group, instead, demonstrated a discontinuous adherence to treatment, by reported an adherence >85% only from second to forth week. Overall, the whole group presented a good adherence (>82%) from the second to the eighth week of treatment (for details, see **Table S2**).

Ad-hoc questionnaire on barriers possibly experienced at home reported positive data.

People reported to have encountered very few barriers during their experience of HEAD telerehabilitaiton. In particular, all participants were motivated to carry out rehabilitation as mean score of motivation barriers was 0.03 ± 0.13. Also, from a logistical point of view, the presence of the technological kit in one's home was not perceived as burdensome, as suggested by the low mean score of logistical barriers: 0.31 ± 0.36. Another positive result was that people could perform activities in autonomy: although sometimes preparation of technological setting needed help from the caregiver, performing activities did not. In fact, we collected a mean score of autonomy barriers of 0.31 ± 0.44. Furthermore, HEAD rehabilitation resulted well-integrated into patients' routine: we reported a mean score of 0.40 ± 0.30 at inclusion in the routine barriers. Finally, technological problems represented the only barrier that sometimes impeded the performance of activities: mean score of technological issues was 0.94 ± 0.73.

Patient-Reported Outcome Measures Results

The whole sample was classified as moderate-to-severe in autonomy in daily routine (d230 ICF domain) and as mild-to-moderate in socialization (d920 ICF domain) at baseline.

We report in **Table 5** percentages of patients who perceived HEAD treatment as successful in their daily living (daily routine and socialization) and who did not, by reporting a change of level of autonomy and socialization in daily life between baseline and after HEAD treatment in all group that experienced ClinicHEAD (Time 1) ($n = 107$) and in the sub-group who additionally experienced HomeHEAD (Time 2) ($n = 38$). We considered as stable or ameliorated patients who presented an ICF score change between time points = 0 or ≤ 1, such as a perceived successful effect of HEAD treatment. On the contrary, patients were considered as worsened when they reported an ICF score change ≥ 1.

We did not find differences for T1-baseline measures between ClinicHEAD and HomeHEAD group (d230: $p = 0.476$; d920: $p = 0.278$).

ClinicHEAD: Results showed a high percentage of people with PD (97%) who reported a perceived maintenance or amelioration of functioning in daily life after 12 sessions of HEAD treatment in clinic. Also, a high percentage of patients with stroke judged a positive influence of HEAD treatment on participation in daily living (82%) and a discrete part of the group extended this perception to performance in daily routine (74%). We didn't find similar results in MS group, in which only 59% of patients perceived a successful effect of treatment. In general, a significantly higher number of people who perceived treatment as successful on daily life functioning was registered than people who did not ($p < 0.001$). This latter result appeared evident in PD and stroke groups, but not in the MS group.

HomeHEAD: We observed satisfying results in the PD group after experience at home. In fact, the entire group (100%) judged a successful effect of HEAD on daily routine and 80% of the sample referred to same perception in daily participation after telerehabilitation. Also the stroke group, which showed positive reported outcome after ClinicHEAD rehabilitation, indicated positive results after rehabilitation at home, with 82% of patients registering a positive effect of telerehabilitation on daily routine and 73% reporting benefits also on participation. Interestingly, the MS group, reported positive results in more than 80% of the group in both daily routine and participation after telerehabilitation at home. In general, we found a significant number of patients reporting positive effect of HEAD treatment on daily functioning (d230: $p < 0.001$; d920: $p = 0.003$).

DISCUSSION

We tested efficiency of HEAD, a new technology enabled rehabilitation program for the continuity of care at home for people with CNDs, such as PD, MS, and chronic stroke based on key performance indicators. In particular, we explored HEAD usability and acceptability together with patient's adherence to treatment, and PROMs, as perceived functioning in routine and participation in daily life. We observed output and outcome measures in clinic for a training duration of 1-month (12 sessions) and in continuity of care at home for a total duration of 3-months (60 sessions).

TABLE 4 | Total adherence to HEAD telerehabilitation along 3-months of treatment at home.

	W1	W2	W3	W4	W5	W6	W7	W8	W9	W10	W11	W12
Adherence %												
PD	0.64	**0.80**	**0.87**	**0.96**	**0.93**	**0.93**	**0.93**	**0.89**	**0.84**	0.78	**0.80**	0.67
MS	0.66	0.79	**0.88**	**0.83**	0.68	0.67	0.71	0.69	0.65	0.57	0.55	0.43
Stroke	**0.80**	**0.92**	**0.92**	**0.92**	**0.90**	**0.87**	**0.88**	0.79	0.74	0.77	0.62	0.57
Whole group	0.71	**0.84**	**0.89**	**0.89**	**0.82**	**0.81**	**0.83**	0.78	0.74	0.69	0.64	0.55
Activities/session												
PD	3.73	4.14	3.64	4.09	3.55	3.95	4.02	3.98	4.03	4.51	4.47	4.23
MS	4.12	4.26	4.04	4.15	4.05	4.20	4.24	4.27	4.18	4.35	4.27	4.58
Stroke	3.52	3.58	3.60	3.35	3.26	3.35	3.25	3.20	3.13	3.00	2.65	2.94
Whole group	3.78	3.97	3.77	3.84	3.59	3.79	3.80	3.80	3.74	3.87	3.77	3.85

MS, multiple sclerosis; PD, Parkinson Disease; W, week; %, percentage. Adherence > 80% is reported in bold.

Our results highlighted a very high compliance rate in all three patient groups in clinic, with 92% adherence to treatment. This data is extremely relevant given that Evidence-Based Medicine guidelines reported 80% as minimum rate of adherence needed to appraise quality of clinical trials (42). In particular, we found that stroke patients followed on average 94% of sessions, whereas the numbers were 93 and 90% for PD and MS, respectively. This positive data can be explained by two main factors. First, the ease of use of the technological system can have affected participation to treatment. In fact, from the point of view of usability, our patients judged the system in clinic as efficient. This is particularly important, since the potential effect of DH is strictly related to the perceived ease of use of health care systems (43, 46). Also, investigating perceived acceptability together with usability of the system we reported satisfying feedbacks regarding HEAD technology acceptance in all three pathologies. Especially, facility of use, usefulness of the program, a good control of the system, perception of relevance on their everyday life and enjoyment was observed. Second, the modality of implementation of activities can have influenced motivation to treatment. Especially, HEAD activities were presented in a VR setting and recent evidence has supported the role of VR in influencing outcome by adhering to basic principles of rehabilitation such as intensity, environment, bio-feedback and motivation (47). Moreover, each activity was embedded in a multimedia content, consisting of short video clips, thought to be motivating for patients. Video clips have historically been used to elicit emotion and motivate people, and their dynamic nature appears to be useful in eliciting interest as well as providing an optimal artificial model of reality (48–50).

Having demonstrated the efficiency of the HEAD program in clinic, we focused also on efficiency of the system during telerehabilitation at home for 3-months. Usability and acceptance of HEAD system at home was high in the whole sample, suggesting a good functionality of the system in telerehabilitation. The high score of sub-domain "Enjoyment" of TAM-3 supported the motivating feature of the rehabilitation activities, probably due to variability of the contents included in activities during 3-months of rehabilitation. Moreover, the game-setting of the rehabilitative activities probably played a crucial role in enjoyment and consequently in acceptance of DH-treatment. Accordingly, a recent study demonstrated that game elements affect duration of enjoyment during motor exercises (51). Also, focusing on adherence, <8% of patients did not complete the entire treatment program. This is an important result since continuity of care is crucial in order to do not lose functional recovery after discharge to home (52, 53). However, while the mean adherence to treatment was over 80% in all 3 patients' groups in the first 2-months, it was lower in the last month of the program. This may be due to the high intensity of the home program: the HEAD program was administered 5 sessions/week for 3-months while Kim's et al. (19) work indicated a maximum of 2–3 sessions per week in the MS population. When considering 3 sessions/week as ideal adherence over time, we found a globally longer persistence over telerehabilitation weeks, with, for example, high adherence over 11 weeks/12 in PD group. Moreover, we observed different patterns of adherence in distinct pathologies: with a better adherence in PD and stroke than in MS. This lower adherence to treatment of the MS group might be due to the fatigue that this population experiences during treatment and in daily life (54). It is known that MS patients are faced with elevated challenges when following long-term intervention and there is an urgent need of future research focusing on solutions for continuity of care and exercise persistence in the MS population (55, 56). Moreover, we considered the implication of the video contents included in HEAD activities: movie clips were collected from historically famous movies of years 1940–1990 (obtained by RAI, Italian Radio Television s.p.a.) with the purpose to stimulate positive memories of patients and as such they may have been more targeted to an older audience. The younger age of the MS group compared to the other two pathologies may have contributed to the perception of these contents as not engaging enough. This result stresses the importance of tailoring contents of rehabilitation to age of population targeted, further studies are needed to better elucidate this issue.

A DH approach is not without barriers. Moving the rehabilitation context outside the clinic can result in difficulties

TABLE 5 | Changes in autonomy (d230) and participation (d920) after ClinicHEAD and after HomeHEAD.

	ICF category	T	ICF qualifier (%)					T1 vs. T0			T2 vs. T0*		
			No problem	Mild problem	Moderate problem	Severe problem	Complete problem	Stabilization /amelioration %	Worsening %	*p*	Stabilization /amelioration %	Worsening %	*p*
PD	d230	0	23.3	20.0	40.0	16.7	0.0	0.97	0.03	**<0.001**	1.00	0.00	–
		1	33.3	30.0	26.7	10.0	0.0						
		2*	36.4	45.5	9.1	9.0	0.0						
	d920	0	33.3	16.7	33.3	16.7	0.0	0.83	0.17	**<0.001**	0.80	0.20	0.114
		1	37.9	20.7	27.6	13.8	0.0						
		2*	36.4	18.2	27.3	18.1	0.0						
MS	d230	0	22.6	19.4	35.5	19.4	3.1	0.59	0.41	0.441	0.89	0.11	**0.045**
		1	13.9	17.2	44.8	17.2	6.9						
		2*	25.0	41.7	33.3	0.0	0.0						
	d920	0	30.0	26.7	20.0	20.0	3.3	0.63	0.37	0.359	0.82	0.18	0.070
		1	24.2	17.2	37.9	20.7	0.0						
		2*	33.3	33.3	16.7	16.7	0.0						
STROKE	d230	0	11.1	37.8	26.7	17.8	6.6	0.74	0.26	**0.002**	0.82	0.18	0.070
		1	18.3	29.5	29.5	18.2	4.5						
		2*	16.7	33.3	33.3	16.7	0.0						
	d920	0	31.8	20.5	22.7	22.7	2.3	0.82	0.18	**<0.001**	0.73	0.27	0.228
		1	35.6	15.6	26.7	15.6	6.5						
		2*	33.4	8.3	33.3	25.0	0.0						
ALL	d230	0	17.9	27.4	33.0	17.9	3.8	0.77	0.23	**<0.001**	0.90	0.10	**<0.001**
		1	21.4	26.2	33.0	15.5	3.9						
		2*	25.7	40.0	25.7	8.6	0.0						
	d920	0	31.7	21.2	25.0	20.2	1.9	0.79	0.21	**<0.001**	0.78	0.22	**0.003**
		1	33.0	17.5	30.1	16.5	2.9						
		2*	34.3	20.0	25.7	20.0	0.0						

*d230, Carrying out daily routine; d920, Recreation and participation; ICF, International Classification of Functioning; MS, Multiple Sclerosis; PD, Parkinson Disease. *, HomeHEAD group (n = 38); %, percentage.* $p_s < 0.05$ *are reported in bold.*

for patients to manage technology systems on their own and include treatment in their daily routine. We evaluated the frequency of patients' experience of the most common barriers during 3-months of tele-treatment. Patient feedback suggested that all participants were highly motivated, that they included HEAD program in their routine, did not encounter logistical problems and were able to conduct rehabilitation activities in autonomy. The overall positive judgments support the suitability of DH in a context of global transition of CNDs rehabilitation treatment from inside to outside the clinic (57). The only barriers encountered were technology problems, probably due to the innovative features of the technology system. This is likely an obstacle that will be solved in the near future since technology transformation over time will lead to increasingly more tailored and useable systems.

Moving from efficiency to focus on PROMs enabled us to deepen our understanding of patient perceptions regarding effectiveness of treatment on their functioning in everyday life. Recent works recommended the application of these measures as extremely informative (27), especially in the investigation of effects of newly implemented DH treatments that often are conducted in a home-based context. In the present study a consistent number of subjects referenced a positive effect of treatment particularly on performance of activities in daily life (90%) and socialization (78%). Interestingly, we found a maintenance or amelioration of functioning in daily living especially high after treatment at home, with a greater number of patients reporting positive effect on autonomy in their routine after telerehabilitation at home vs. rehabilitation treatment in clinic (90% of subjects vs. 78%). This evidence is crucial, in accordance with suggestion of Steinhubl et al. (58), who, reporting definitions and scenarios fostered by the new mobile health technologies, declare that changes in the care environment are able to provide better outcomes. More importantly, this result is in line with the main goal of rehabilitation itself, that aims at the recovery of the patient's functioning in terms of its utilization in daily living; all in the overall context of the biopsychosocial digital model that foresees a collaboration between clinicians and patient facilitated by DH in the social context of the person (9). Considering socialization in daily life, we found different outcome in the three pathologies. There was a better perception of socialization after the in-clinic HEAD program than following the home telerehabilitation program. On

the contrary, MS patients showed an increase in socialization after telerehabilitation at home compared to the clinic. This result may be related to the phenomenon of the baby boomer generation: people born between 1946 and 1964 need to be introduced to technology. Instead, younger people, nearer to millennials, are more familiar with technology systems. Hence, our results could be explained by demographic factors of our population targets: patients with an older age, such as those with PD and stroke, appreciated HEAD potential benefit on socialization more in clinic setting than at home, while younger people, such as the MS sample in our study, are able to report treatment potentiality on their daily life when it is fostered in their home setting.

Targeting three pathologies, MS, PD, and Stroke in this study leads to smaller sample size for each group which could constitute a limitation. However, one of the hallmarks of the proposed study is its adaptability to different functional levels and its suitability for different neurological disorders. In fact, one of the problems other studies have faced in the past is the narrow applicability of their intervention systems (59). The HEAD protocol is developed to overcome this problem. This study proposes to investigate the responsiveness of the tested intervention to the needs of diverse populations with chronic neurological pathologies that are typically seen in rehabilitative practices and need to have access to monitored continuity of rehabilitative activities.

While the sample size of this study is too small to draw conclusive evidence of the efficacy of the proposed intervention, the results support HEAD as a useful and acceptable DH-care system for people with CNDs with positive impacts on the perceived benefits for autonomy and daily life involvement. This is important given the crucial role technology will play in future neurorehabilitation models. Our findings support the notion that intensity and duration of long-term intervention must be tailored to the individual, taking into account also the personalization of contents to maintain an adequate level of engagement in rehabilitation at home.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committees of IRCCS Don Gnocchi Foundation, of inter-company of the province of Lecco, Como and Sondrio, and of inter-company "Città della Salute e della scienza" of Turin. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

FB, FM, and MS conceived the study. CG, JJ, and PG carried out the study. CC, CP, and GP collected data. CP, SI, and FB performed statistical analysis and interpreted results. FB, JJ, and SI wrote the manuscript. All authors reviewed and approved the final manuscript.

FUNDING

This study had been funded by the Fondazione Cariplo, Italy. This funding source had no role in the design of this study and will not have any role during its execution, analyses, interpretation of the data, or decision to submit results.

ACKNOWLEDGMENTS

We would like to thank all patients who participated to the study. We would also thank the HEAD study group to make possible to conduct the present study (alphabetic order): Aggujaro S, Barra G, Bellomo M, Bertoni R, Boccini S, Bonanima M, Borgogno P, Bowman T, Canobbio S, Castagna A, Covarrubias M, Del Principe A, Di Tella S, Enei L, Ferrari A, Ferrarin M, Fini M, Gencarelli N, Giordano A, Manfredini C, Marino C, Martina L, Mendozzi L, Mocarelli P, Montesano A, Nemni R, Perini G, Peverelli M, Proserpio D, Pugnetti L, Ripamonti E, Rossini M, Ruffin G, Saibene FL, Trombini D, Zanfini A.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2019.01206/full#supplementary-material

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

ORIGINAL RESEARCH
published: 27 January 2020
doi: 10.3389/fneur.2019.01419

Brain Functional Networks Study of Subacute Stroke Patients With Upper Limb Dysfunction After Comprehensive Rehabilitation Including BCI Training

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OPEN ACCESS

Edited by:
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University College London,
United Kingdom

Reviewed by:
Martijn Beudel,
University Medical Center
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Emanuele Spina,
University of Naples Federico II, Italy

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Specialty section:
This article was submitted to Neurorehabilitation, a section of the journal Frontiers in Neurology

Received: 12 July 2019
Accepted: 30 December 2019
Published: 27 January 2020

Citation:
Wu Q, Yue Z, Ge Y, Ma D, Yin H, Zhao H, Liu G, Wang J, Dou W and Pan Y (2020) Brain Functional Networks Study of Subacute Stroke Patients With Upper Limb Dysfunction After Comprehensive Rehabilitation Including BCI Training. Front. Neurol. 10:1419. doi: 10.3389/fneur.2019.01419

Brain computer interface (BCI)-based training is promising for the treatment of stroke patients with upper limb (UL) paralysis. However, most stroke patients receive comprehensive treatment that not only includes BCI, but also routine training. The purpose of this study was to investigate the topological alterations in brain functional networks following comprehensive treatment, including BCI training, in the subacute stage of stroke. Twenty-five hospitalized subacute stroke patients with moderate to severe UL paralysis were assigned to one of two groups: 4-week comprehensive treatment, including routine and BCI training (BCI group, BG, $n = 14$) and 4-week routine training without BCI support (control group, CG, $n = 11$). Functional UL assessments were performed before and after training, including, Fugl-Meyer Assessment-UL (FMA-UL), Action Research Arm Test (ARAT), and Wolf Motor Function Test (WMFT). Neuroimaging assessment of functional connectivity (FC) in the BG was performed by resting state functional magnetic resonance imaging. After training, as compared with baseline, all clinical assessments (FMA-UL, ARAT, and WMFT) improved significantly ($p < 0.05$) in both groups. Meanwhile, better functional improvements were observed in FMA-UL ($p < 0.05$), ARAT ($p < 0.05$), and WMFT ($p < 0.05$) in the BG. Meanwhile, FC of the BG increased across the whole brain, including the temporal, parietal, and occipital lobes and subcortical regions. More importantly, increased inter-hemispheric FC between the somatosensory association cortex and putamen was strongly positively associated with UL motor function after training. Our findings demonstrate that comprehensive rehabilitation, including BCI training, can enhance UL motor function better than routine training for subacute stroke patients. The reorganization of brain functional networks topology in subacute stroke patients allows for increased coordination between the

multi-sensory and motor-related cortex and the extrapyramidal system. Future long-term, longitudinal, controlled neuroimaging studies are needed to assess the effectiveness of BCI training as an approach to promote brain plasticity during the subacute stage of stroke.

Keywords: brain computer interface, resting state functional magnetic resonance imaging, stroke, neural plasticity, functional connectivity

INTRODUCTION

Recovery of upper limb (UL) motor function after stroke is a critical step for a patient to recover daily activities. Most stroke survivors have acute-stage UL dysfunction, although recovery is incomplete for many (1). Recovery of full UL function is achieved by only 18% of patients who initially present with severe paresis. Furthermore, about 60% of patients with nonfunctional UL at 1 week post-stroke do not fully recover even after 6 months (2). UL dysfunction significantly limits an individual's participation in both physical and social activities (3).

Motor network reorganization after stroke is time- and activity-dependent (4). Hebbian plasticity describes the phenomenon of coincident activation of pre- and post-synaptic neurons, leading to a reinforcement of synaptic strength, finally resulting in increased and more reliable communication between the activated neurons (5, 6). The potential relevance of this concept in behavioral change is particularly well-illustrated in the context of stroke rehabilitation (7). Assuming that the connection between the peripheral muscles and sensorimotor cortex has been disrupted due to the formation of a cortical or subcortical lesion, concurrent activation of sensory feedback loops, combined with activation of the primary motor cortex, may lead to the reinforcement of previously dormant cortical connections via Hebbian plasticity, thereby supporting functional recovery (8, 9). Therefore, it is necessary to develop therapeutic approaches focused on skill learning to promote plasticity, involving enhanced activity of the motor cortex (10). Brain computer interface (BCI) systems allow the brain signals to provide both physical assistance and recovery following central nervous system injury by providing users with brain state-dependent sensory feedback via functional electrical stimulation, virtual reality environments, or robotic systems (11–14). BCI systems can also be used to detect real-time primary motor cortex activation, i.e., the intention to move. As particularly relevant input to BCI systems, EEG signals have highly accurate temporal resolution, are suitable to clinical environments, and can provide matched sensory stimulation according to specific feedback protocols (15, 16). Hence, BCI systems used for motor neurorehabilitation can induce activity-dependent plasticity in specific areas of the brain by requiring the user to pay close attention during task-oriented training, which activates sensorimotor areas (9, 17, 18).

EEG-based BCI strategies have been recently proposed as a promising stroke neurorehabilitation strategy to treat symptoms, including paralysis, cognitive disorders, and aphasia (19–25). Despite the large heterogeneity in the available literature, there is consensus that BCI-based training can help to improve UL motor function in stroke patients.

This is exemplified in the work undertaken by Ramos-Murguialday (26). As compared to placebo expectancy, where orthosis movements occur randomly, significant improvements following BCI training are suggestive of a clinically relevant change from no activity to some voluntary movement of paretic muscles. The electromyography activity of the paretic UL has been correlated to changes in the laterality index, as assessed by fMRI.

However, previous studies do not take account of clinical significance, nor examine clinical effect by of minimal clinically important differences (MCID). MCID signifies smallest change in an outcome measure and can be detected beyond the measurement error. Jaeschke first defined MCID as being "the smallest difference in score in the domain of interest which patients perceive as beneficial and which would mandate, in the absence of troublesome side effects and excessive cost, a change in the patient's management" (27). It is an objective as well as a statistical attribute. Patients who experience an estimated MCID score are more likely to experience a meaningful improvement in disability level than those who do not (28). Researches involved BCI would have been more constructive to clinicians if more attention was paid to MCID.

In addition, another pathway to verify the effectiveness of BCI is to correlate clinical scores with function monitoring. Resting state (rs)-fMRI is used to identify the connectivity traits within the brain that are presumed to be related to neuronal cooperation (29). Many studies have utilized rs-fMRI to measure the activity, spatial extent, and integrity of common measures of FC, such as the default mode network and the sensorimotor network (12, 19, 30–32). Increasing numbers of studies have investigated changes in FC that correlate with motor improvements following BCI training.

In 2013, Várkuti analyzed longitudinal data to examine individual gains in long-term clinical improvements related to FC and demonstrated that increased FC of the supplementary motor area, motor cortex, visuospatial system, and cerebellum was correlated with improved UL function. In other words,

Abbreviations: BCI, Brain Computer Interface; UL, Upper Limb; FMA-UL, Fugl-Meyer Assessment-UL; ARAT, Action Research Arm Test; WMFT, Wolf Motor Function Test; FC, Functional Connectivity; EEG, Electroencephalography; EMG, Electromyography; fMRI, Functional Magnetic Resonance Imaging; TSS, Time Since Stroke; MAS, Modified Ashworth Scale; tDCs, Transcranial Direct Current Stimulation; TMS, Transcranial Magnetic Stimulation; DBS, Deep Brain Stimulation; BOLD, Blood Oxygen Level Dependent; MNI, Montreal Neurological Institute; FWHM, Full-Width-Half-Maximum; ROI, Regions of Interest; BA, Brodmann Area; MCID, Minimal Clinically Important Differences.

changes in FC may be predictive of motor improvement. The authors recommend that future training attempts should focus on directly inducing these beneficial changes (19). One advantage of this study was analysis of the cerebellum, which is often ignored. However, since significant voxels were identified across two groups, the predictors of functional gains in motor function from FC change maps might only represent adaptive processes occurring in the recovering brain, rather than BCI-specific changes.

Young described whole brain network changes correlated with motor recovery following BCI and suggested that the average motor network FC seeded in the thalamus (mainly involving the precuneus, cingulate, paracentral lobule, cerebellum, and superior and middle frontal gyri) was increased mid-therapy and post-therapy relative to baseline. The correlations between FC and behavioral outcomes indicate that both adaptive and maladaptive changes may develop with BCI training (30). However, the study failed to draw a distinction between general increases in FC and non-motor-related FC, which may reveal other neuro-modulatory components of BCI training.

Additionally, machine learning classification was applied to identify the stages of BCI training most beneficial for stroke rehabilitation. Researchers found that regions beside the motor network, such as FCs in fronto-parietal task control, the default mode network, and the subcortical and visual networks, showed similar changes after BCI training. Both strengthening and weakening of FCs were found to be involved in motor and non-motor regions. This study provided new evidence to support the potential clinical utility of BCI training, which not only benefits motor recovery, but also facilitates recovery of other brain functions (32). Furthermore, the study highlighted how machine learning can provide useful information by correlating neuro-function changes (i.e., rs-fMRI, EEG) to behavioral changes (i.e., Action Research Arm Test, Nine-Hole Peg Test, and Barthel Index). They also found that FCs related to the bilateral primary motor area were correlated to behavioral outcomes and clinical variables (33).

BCI-based training can be considered a type of motor learning to modify neuronal activities through sustained feedback and reward. Studies have identified feedback and reward as important contributors to neurorehabilitation (34–37). However, the relationship between BCI training and feedback/reward-related regions of the brain has not been extensively investigated; thus, the efficacy and mechanisms of BCI-based training remain unclear, such as the effects on subacute stroke patients, alterations to sensorimotor area-related networks, and precise relationships with UL function.

Studies have confirmed the clinical benefits of BCI training and brain functional plasticity of UL function in chronic stroke patients. However, in a real world study, most stroke patients engage in rehabilitation with multiform treatments in the subacute stage. However, changes to neural networks in the subacute stage are unclear. As an exploratory study of long-term, controlled research, the aim of the present study was to identify topological alterations in brain functional networks following comprehensive treatment, including BCI training, in subacute stroke patients.

Based on previous studies, we hypothesized that (a) after comprehensive treatments, including BCI training, patients with subacute stroke would develop regional and network topological alterations involving typical hand-related motor regions, as well as sensory/atypical regions; and (b) that these alterations in neural activities would correlate to clinical UL motor function scores.

MATERIALS AND METHODS

Ethical Approval

The study protocol was approved by the Ethics Committee of Beijing Tsinghua Changgung Hospital (Beijing, China) and conducted in accordance with the tenets of the Declaration of Helsinki (approval no. 18172-0-02). All patients provided written informed consent prior to study participation. This study is registered at http://www.chictr.org.cn under the study identifier ChiCTR1900022128.

Subjects

The study cohort consisted of 25 subacute stroke patients who were recruited from the Department of Physical Medicine and Rehabilitation of Beijing Tsinghua Changgung Hospital (Beijing, China). Each patient underwent a full neurological examination to exclude any accompanying neurological disorders considered as exclusion criteria.

Inclusion Criteria

Patients considered for study inclusion met all of the following criteria: (1) age, 18–75 years; (2) sufficient cognition to follow simple instructions and understand the purpose of the study (Mini Mental State Examination, MMSE score >21); (3) hemiparesis resulting from a unilateral brain lesion, as confirmed by MRI, with a time since stroke (TSS) of 1–6 months prior to study enrollment; (4) moderate-to-severe UL paralysis, as determined by a Brunnstrom score ≤ IV; and (5) Modified Ashworth Scale (MAS) score <3.

Exclusion Criteria

The exclusion criteria were as follows: (1) severe hand spasticity (MAS score ≥ 3); (2) open wound or deformity of the affected UL; (3) visual field deficit; (4) severe cognitive deficit or receptive aphasia; (5) heavy medication affecting the central nervous system; (6) concomitant serious illness; (7) unilateral spatial neglect; (8) severe dystonia and/or involuntary movements; (9) other neurological disorders, such as severe epilepsy; and (10) participation in another brain stimulation project, such as transcranial direct current stimulation, transcranial magnetic stimulation, or deep brain stimulation, during the training period.

Baseline Assessment

Baseline clinical scoring included Fugl-Meyer Assessment of the ULs (FMA-UL) (38), the Wolf Motor Function Test (WMFT), and the Action Research Arm Test (ARAT) (39). This study was a randomized control trial of indications employed in previous

pilot studies to evaluate the effectiveness of novel rehabilitative interventions (40). The patients were enrolled sequentially and assigned to either the BG or the CG with the use of a pre-designed random number sequence list. Appropriate adjustments were made to balance scores of the most important covariates (i.e., baseline Brunnstrom score, age, sex, TSS, affected hemisphere, type of the lesion, and lesion location). The appointed therapist in charge of the clinical assessment was blinded to the mode of training received by the patients throughout the study period.

Comprehensive Rehabilitation

All patients received standard medical care and rehabilitation for 4 weeks, which consisted of routine physiotherapy and occupational therapy focused on rehabilitation of arm and hand movements used in daily activities, such as grasping a toothpaste tube, eating, reaching, and grasping while sitting and standing. Each treatment session lasted 2 h in the CG and 1 h in the BG per day, 5 days per week.

On the base of routine training, a BCI training system was developed in the BG, as shown in **Figure 2**. EEG signals were recorded using eight dry electrodes, and then amplified (g.LADYbird, g.Tec Medical Engineering GmbH, Schiedlberg, Austria) and computer processed. A video was projected onto a screen to guide the patient in order to complete each training task. An exoskeleton hand was used to assist the paretic hand in grasping/opening exercises, based on the results of the mu suppression algorithm that was calculated from the EEG signals (41). The system also displayed a mu suppression score on the screen to provide real-time feedback. The mu suppression score provides information about the degree of motor innervation, allowing the patient to adjust in order to achieve higher scores.

EEG signals were referenced to a unilateral earlobe and grounded at the other earlobe. The signal from eight active electrodes was sampled at 256 Hz. EEG signals were also processed in real-time by the amplifier using a band-pass filter (2–60 Hz) and a notch filter (48–52 Hz) to remove artifacts and power line interference, respectively. The EEG electrodes were placed over the central area according to the International 10–20 system (FC3, FC4, C3, C4, CP3, CP4, C1, C2). EEG signals from the C3 and C4 electrodes were used for BCI control. Furthermore, some of the sites related to motor function were used for offline analyses (left hemisphere: FC3, C3, and CP3; right hemisphere: FC4, C4, and CP4). FC3/FC4 covered over the premotor cortex, while C3/C4 covered over the primary motor cortex. CP3/CP4 corresponded to the supramarginal gyrus, which is part of the somatosensory association cortex. These electrodes covered the majority of the sensorimotor cortex.

To compute the mu suppression, the EEG data from C3 to C4 were converted to the frequency domain by a Fourier transform algorithm with a Hanning window covering the EEG data during the video period of the paradigm. The mean power of the mu band (8–13 Hz) for the selected electrode was calculated. Mu suppression reflects an event-related desynchronization of the EEG caused by an increase in neural activity (42). The mu suppression score was calculated according to the following equation (43): where Mu Supp is the Mu suppression score, Mutast is the mu power of the EEG during the motor imagery (MI) task state, and Mu_{rest} is mu power of EEG during the resting state.

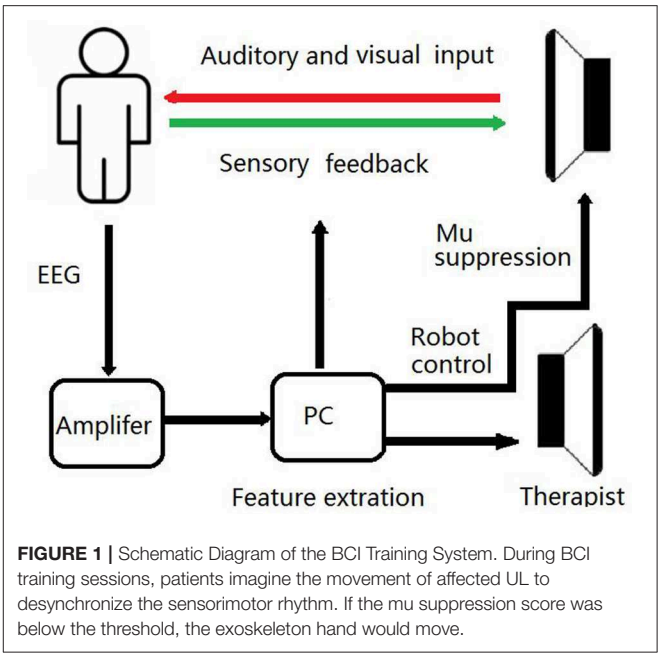

FIGURE 1 | Schematic Diagram of the BCI Training System. During BCI training sessions, patients imagine the movement of affected UL to desynchronize the sensorimotor rhythm. If the mu suppression score was below the threshold, the exoskeleton hand would move.

$$\text{Mu}supp = -\frac{Mup_{task} - Mup_{rest}}{Mup_{rest}} * 100$$

BCI Training and Paradigms

Patients in the BG received a total of 20 BCI training sessions, lasing for 1 h per day, 5 days per week, for 4 weeks. During the BCI training sessions, patients were instructed to imagine the movement of their affected UL in order to desynchronize sensorimotor rhythm and then to imagine grasping or releasing a cup with the affected hand, after an image-inverted video taken prior of the unaffected hand (**Figure 1**). The mu suppression score was calculated based on EEG signals during the video clip. An exoskeleton hand provided support to assist the patient with the completion of the hand grasping/opening task during the following 3 s. If the mu suppression score was continuously below the calculated threshold in the motor intention classification area, the exoskeleton hand would move. During each session, the trial was repeated 100 times, and video of the grasping and opening hand was shown alternately at random. Patients were allowed to rest for 1 min after every 10 trials. Patients were instructed to avoid blinking, coughing, chewing, and any other head and body movements.

Functional Magnetic Resonance Imaging

All fMRI data of the BG were acquired using a GE 3.0T MR scanners (Discovery^{TM} MR750; GE Healthcare Life Sciences, Chicago, IL, USA) before and after training. Participants were scanned in the supine position using a standard 32-channel head-coil. fMRI parameters for rs Blood Oxygen Level Dependent (BOLD) images were an "Ax-BOLD rest" series using a gradient

echo planar-imaging sequence, with the following parameters: repetition time = 2,000 ms, echo time = 30 ms, flip angle = 90°, pixel space = 3.5 mm^2, slice thickness = 3.5 mm, spacing between slices = 4 mm, acquisition matrix = [64, 0, 0, 64] (equivalent to an in-plane resolution of 64 × 64), reconstruction diameter = 224 mm, 34 axial slices, and 240 temporal positions. T1-weighted images (T1) were a "Sag 3D T1BRAVO" series, with repetition time = 8.21 ms, echo time = 3.18 ms, flip angle = 8°, vocal space = 1 mm^3, spacing between slices = 1 mm, acquisition matrix = [0, 256, 256, 0] (equivalent to 256 axial slices and 256 coronal slices). The sagittal slice number depended on the head size of each patient, and ranged from 156 to 174 mm. The reconstruction diameter was 256 mm.

FC Analysis

Neuroimaging assessment of FC of the BG was performed by rs-fMRI in three steps: preprocessing, brain network construction, and network feature analysis.

Step 1 was rs BOLD signal preprocessing, which was performed using DPARSFA version 3.2 (http://www.rfmri.org/DPARSF). The first 10 temporal positions of data were discarded to familiarize the patient with the scanning environment. For all remaining temporal positional data. Slice timing correction was performed by phase shifting. The reference slice was set to the slice acquired at the middle time point. Then, head motion was corrected, followed by normalization to the Montreal Neurological Institute (MNI) space with 3 mm isotropic pixel resampling with the direct use of the EPI template. Preprocessing in MNI space included smoothing the data with 4 mm full width at half maximum, while removing the linear trend of the time course, and nuisance covariance regression with head motion, white matter, cerebral fluid, and the whole-brain global signal. Finally, the signal was temporally filtered at a frequency of 0.01–0.08 Hz using an ideal rectangular filter.

Step 2 was brain network construction. We adopted a brain atlas combined with the Brodmann atlas and AAL. This atlas was constructed by appending the cerebellum mapping in AAL (areas 91–116) to the Brodmann atlas (**Figure 2**). Each area was considered a node in the brain network. At each temporal position, within each area, the average BOLD signal was assigned to the node as the signal intensity. The correlation coefficient between each pair of nodes was calculated as the FC between two regions.

Stroke-related damage to brain tissues may lead to issues during fMRI processing and FC measurements (44), including registration errors and signal disruption. We smoothed data during preprocessing and applied a brain atlas to define the nodes. Smoothing and signal averaging mitigated slight displacement of registration, gave that one region typically contains hundreds- thousands of voxels and smoothing and averaging could blur boundaries. One main issue related to signal disruption is hemodynamic lags. In our work, the patients were in the subacute stage, and according to Siegel, the prevalence of patients showing substantial hemodynamic lags decreases as TSS increases (44). Besides, FC alterations induced by hemodynamic lags following stroke could be taken as a feature of stroke patients, thus it is meaningful to investigate how this feature changes after rehabilitation treatment.

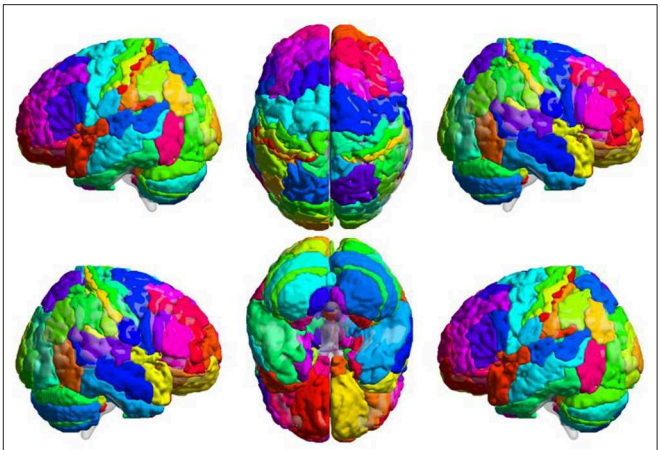

FIGURE 2 | Combined Brain Atlas of the Brodmann Atlas and AAL. Brain atlas was constructed by appending the cerebellum mapping in AAL to the Brodmann atlas. Each colored area presents a functional node in the brain network. This illustration was visualized using BrainNet Viewer (https://www.nitrc.org/projects/bnv/).

Step 3 was network feature analysis. To investigate network alterations of the BG, seed-based inter-regional correlation analysis was performed. Connections that increased after treatment were identified. The FC was correlated with clinical scores.

Regions of Interest (ROIs)

ROIs were positioned at the main sensory and motor related cortices that were the source of EEG signals, including the bilateral primary somatosensory cortices (BA1, BA2, BA3), primary motor cortex (BA4), somatosensory association cortex (BA5), premotor cortex (BA6), and superior parietal lobule (BA7). FC changes between the ROIs relative to the whole brain were investigated. Furthermore, the internal relationships between clinical changes and functional reorganization of patients in the BG were explored.

Outcome Measures

Primary Outcome Measures

FC between regions and the whole brain of the BG was the major outcome measure used to detect functional reorganization.

Secondary Outcome Measures

The secondary outcomes in this study included the following data of both groups. Demographic data including age and TSS were considered minor (secondary) measures. Clinical score including FMA-UL, ARAT, WMFT before and after training was also secondary measures used to assess changes in UL motor function.

Statistical Analysis

All fMRI data were analyzed using NumPy 1.12.1 (http://www.numpy.org) and Scipy 0.19.0 (http://www.scipy.org) software. All demographic and clinical data were analyzed using IBM

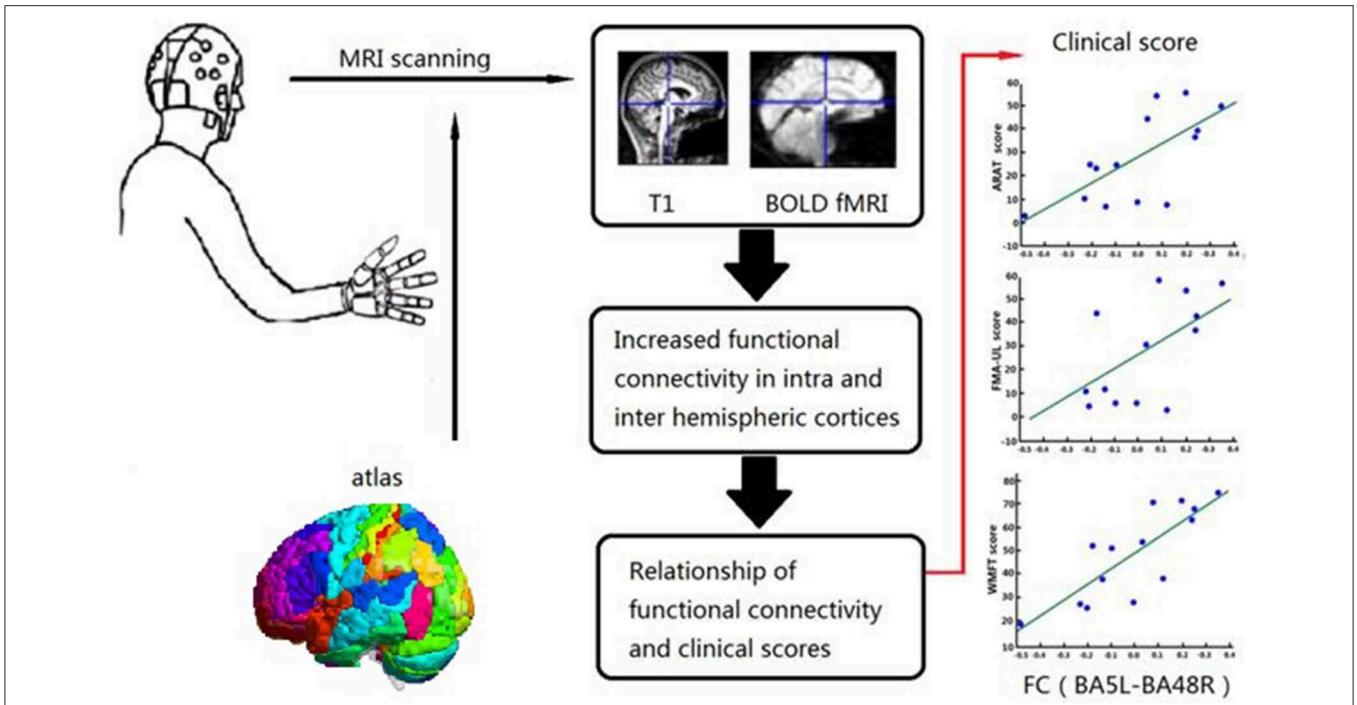

FIGURE 3 | Relationship between Clinical Scores and Functional Alterations. Graphical abstract of this study, patients were assigned to one of BG and CG. Functional assessments of both groups and FC in the BG were performed before and after 4 weeks training. Relationship of FC and clinical scores were analyzed in BG.

TABLE 1 | Demographic and clinical characters.

Characteristics	BG($n = 14$)	CG($n = 11$)	$t/Z/\chi^2$	*P*
Age (years)	62.93 ± 10.56	64.82 ± 7.22	−0.507[c]	0.617
Sex (male: female)	9:5	9:2	0.939[a]	0.332
Affected hand (right: left)	8:6	6:5	0.337[a]	0.561
TSS (month)	2.11 ± 0.30	2.00(1.50, 3.00)	−0.142[b]	0.887
Type(hemo/isch)	3:11	3:8	0.943[a]	0.332
MMSE score	24.29 ± 2.70	25.18 ± 2.86	−0.803[c]	0.430
FMA -UL score	18.43 ± 2.65	14.09 ± 2.51	1.164[c]	0.256
ARAT score	9.50(3.00, 23.25)	1.00(0.00, 10.00)	−1.900[b]	0.057
WMFT score	30.07 ± 3.38	25.09 ± 2.96	1.074[c]	0.294

hemo, hemorrhagic stroke; isch, ischemic stroke; TSS, time since stroke; UL-FMA, Upper-Limb Fugl-Meyer Assessment; ARAT, Action Research Arm Test; WMFT, Wolf Motor Function Test. [a]Chi-square test; [b]Mann–Whitney U test; [c]two-tailed unpaired t-test.

TABLE 2 | Lesion maps of patients.

Affected Vessel	Region	BG ($n = 14$)	CG ($n = 11$)
Middle cerebral artery	Basal ganglia	2	2
	Basal ganglia, PLIC	1	1
	Lateral ventricle	1	1
	Basal ganglia, lateral ventricle	3	1
	Thalamus	1	1
	Subtotal	8	6
Posterior circulation	Pons, brainstem	4	2
Internal carotid artery	Frontal lobe, parietal lobe and temporal lobe	2	3
χ^2	0.804[a]	*P*	0.669

PLIC, posterior limb of internal capsule; [a]Chi-square test of different affected vessel between two groups.

SPSS Statistics for Windows, version 20.0. (IBM Corporation, Armonk, NY, USA). Normally distributed data are expressed as the mean ± standard deviation. Intergroup comparisons were made using the two-tailed unpaired *t*-test, while intra group comparisons were made using the two-tailed paired *t*-test. Non-normally distributed data are expressed as the median and quartile. The Wilcoxon ranked sum test was used for intra group comparisons and the Mann–Whitney *U*-test for inter group comparisons. The chi-square test was used to identify differences in rates among the groups. Spearman's rank correlation was calculated to assess the relationship between clinical score ranking and corresponding FC of the BG. A probability (p) value <0.05 was considered statistically significant for all tests. The entire procedure is shown in **Figure 3**.

RESULTS

Demographics

All of the patients completed training without adverse effects. **Tables 1, 2** reported the clinical feature for all patients (pre

TABLE 3 | Results of clinical scores.

		Pre	Post	Δ
FMA-UL	BG	18.43 ± 2.645	35.357 ± 4.255	16.93 ± 2.560
	CG	14.09 ± 2.513	28.071 ± 4.832	8.36 ± 2.116
	Intra group of BG	**Intra group of CG**	**Inter group pre**	**Inter group post**
t/*Z*-value	−6.612[d]	−2.673[d]	1.164[c]	−2.549[c]
p/Sig. value	0.000*	0.008*	0.256	0.011*
	Intra group of BG	**Intra group of CG**	**Inter group pre**	**Inter group post**
ARAT	BG	9.50 (3.00, 23.25)	28.07 ± 4.83	8.50 (4.75, 24.00)
	CG	1.00 (0.00,10.00)	4.00 (3.00,24.00)	4.00 (0.00, 4.00)
	Intra group of BG	**Intra group of CG**	**Inter group pre**	**Inter group post**
t/*Z*-value	−3.297[b]	−2.555[b]	−1.900[e]	−2.007[e]
p/Sig. value	0.001*	0.011*	0.057	0.045*
	Intra group of BG	**Intra group of CG**	**Inter group pre**	**Inter group post**
WMFT	BG	30.07 ± 3.38	47.79 ± 5.00	17.71 ± 3.34
	CG	25.09 ± 2.96	28.00 (18.00, 50.00)	3.00 (1.00, 14.00)
	Intra group of BG	**Intra group of CG**	**Inter group pre**	**Inter group post**
t/*Z*-value	−5.298[d]	−2.668[b]	1.074[c]	−2.110[e]
p/Sig. value	0.000*	0.008*	0.294	0.035*

*[b] Mann–Whitney U test, [c] two-tailed unpaired t-test; [d] two-tailed paired t-test; [e] Wilcoxon signed-rank test; *p < 0.05.*

TABLE 4 | Functional connectivity between ROI and whole brain network of BG.

ROI	BA	Connected Region	BA	Mean ± SD	Mean ± SD	*t*-value	*P*-value
Primary motor cortex	4L	Primary auditory cortex	41R	−0.008 ± 0.212	0.135 ± 0.227	2.317	0.038
Premotor cortex	6R	Superior parietal lobule	7L	−0.177 ± 0.252	0.049 ± 0.214	3.723	0.003
Premotor cortex	6R	Primary somatosensory cortex	2R	0.489 ± 0.133	0.590 ± 0.141	2.542	0.025
Premotor cortex	6R	Primary somatosensory cortex	3R	0.586 ± 0.232	0.697 ± 0.085	2.321	0.037
Premotor cortex	6R	Lateral occipitotemporal cortex	37L	−0.214 ± 0.183	−0.057 ± 0.213	3.092	0.009
Premotor cortex	6R	Superior parietal lobule	7R	0.045 ± 0.228	0.198 ± 0.270	2.774	0.016
Premotor cortex	6R	Associative visual cortex	19L	−0.207 ± 0.227	−0.013 ± 0.287	2.181	0.048
Primary motor cortex	5L	Putamen	48R	−0.128 ± 0.174	−0.006 ± 0.224	2.204	0.046
Primary motor cortex	5L	Putamen	48L	−0.022 ± 0.224	0.088 ± 0.196	2.185	0.048
Primary motor cortex	5R	Pars opercularis	44L	−0.309 ± 0.131	−0.200 ± 0.152	2.682	0.019

As comparing with the baseline, there were significant increases in FC post-training. L, left hemisphere; R, right hemisphere; BA2, BA3, primary somatosensory cortex; BA4, primary motor cortex; BA5, Somatosensory Association Cortex; BA6, premotor cortex; BA7, superior parietal lobule; BA41, primary auditory cortex; BA37, lateral occipitotemporal cortex; BA19, Associative Visual Cortex; BA44, pars opercularis; BA48, putamen.

and post, respectively). Prior to training, the two groups were statistically homogeneous, as there were no significant demographic differences in age (two-tailed unpaired *t*-test, $p = 0.617$), sex (chi-square test, $p = 0.332$) or affected hand (chi-square test, $p = 0.561$). Similarly, there were no significant differences in TSS (Wilcoxon signed-rank test, $p = 0.887$), lesion type (chi-square test, $p = 0.332$), lesion location (chi-square test, $p = 0.669$) and cognitive impairments (two-tailed unpaired *t*-test, $p = 0.430$). Also, patients in the two groups had similar levels of baseline clinical scores including FMA-UL (two-tailed unpaired *t*-test, $p = 0.256$), ARAT (Wilcoxon rank-sum test, $p = 0.057$), and WMFT (two-tailed unpaired *t*-test, $p = 0.294$).

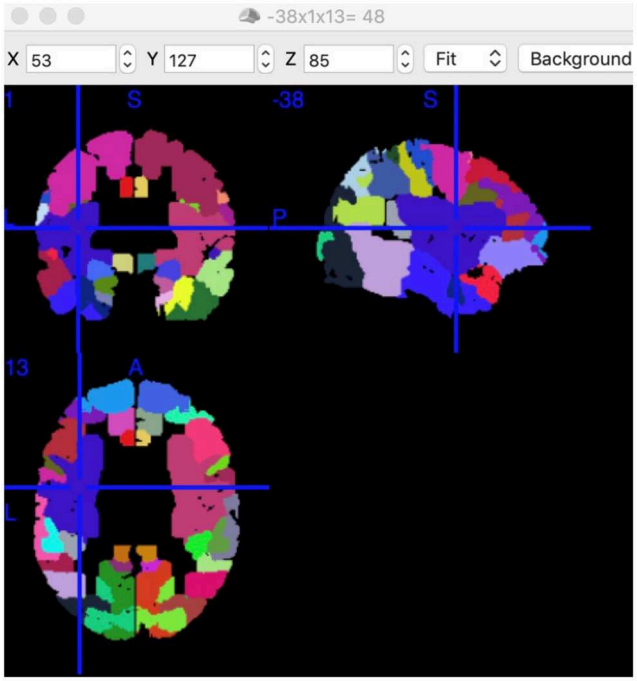

FIGURE 4 | Position of Putamen and BA48. Position of BA48 had a center position on MNI: −38, 1, 13 in this study. Each colored area presents a functional node. This screenshot was captured using MRIcron (https://www.nitrc.org/projects/mricron).

Clinical Outcome Measures

Clinical changes after training were observed, with increased scores of FMA-UL, ARAT, and WMFT of both groups, indicating improved UL motor function (**Table 3**). The intra group differences of both groups after training were statistically significant in all clinical assessments ($FMA\text{-}UL_{BG}$, two-tailed paired t-test, $p = 0.000$; $ARAT_{BG}$, Wilcoxon signed-rank test, $p = 0.001$; $WMFT_{BG}$, two-tailed paired t-test, $p = 0.000$; $FMA\text{-}UL_{CG}$, two-tailed paired t-test, $p = 0.008$; $ARAT_{CG}$, Wilcoxon signed-rank test, $p = 0.011$; $WMFT_{CG}$, Wilcoxon signed-rank test, $p = 0.008$).

The increased ranges in the BG were ΔFMA-UL: 16.93 ± 2.56, ΔARAT: 8.50 (4.75–24.00) and ΔWMFT: 17.71 ± 3.34. The increased ranges of the CG were ΔFMA-UL: 8.36 ± 2.116, ΔARAT: 4.00 (0.00, 4.00) and ΔWMFT: 3.00 (1.00, 14.00), respectively.

Prior to training, the two groups were statistically homogeneous. No significant clinical differences were found in FMA-UL, ARAT, and WMFT between groups. After training, there were significant inter group differences ($FMA\text{-}UL_{BG-CG}$, two-tailed unpaired t-test, $p = 0.011$; $ARAT_{BG-CG}$, Mann–Whitney U-test, $p = 0.045$; $WMFT_{BG-CG}$, Mann–Whitney U-test, $p = 0.035$).

FC Change

In order to avoid mass data dilution, we only analyzed increased FCs of the BG in this study. The two-tailed paired t-test was used to identify significant changes in FC ($p < 0.05$, uncorrected) after treatment. After training, the FCs were found to be increased in the following areas: FC between left BA4 and right BA41, left BA5 and right BA44, and left BA5 and bilateral BA48. BA6 of the right hemisphere was found to be a key brain network node, which connected to left BA37, left BA19, and bilaterally to BA7 (**Table 4**, **Figures 5, 6**).

Notably, every Brodmann area contained many voxels with irregular shapes. The region where increased FC connected with left BA5 had a center position on MNI: −38, 1, 13 (**Figure 4**). According to the Brodmann atlas model, this region corresponded to BA 48 and had a large part to overlap the putamen anatomically.

Correlation Analysis of Increased FCs and Clinical Score

Correlation analysis was performed to assess the relationship between FC and clinical score in the BG (FMA-UL, ARAT, and WMFT scores). After comprehensive rehabilitation, including BCI training, increases in FC between the left BA5 and right BA48 were positively correlated with clinical scores post training: $FMA\text{-}UL_{post}$ score (Spearman's rank correlation, $r = 0.641$, $p = 0.013$; **Figure 7**), $ARAT_{post}$ score (Spearman's rank correlation, $r = 0.701$, $p = 0.005$; **Figure 8**), and $WMFT_{post}$ score (Spearman's rank correlation, $r = 0.814$, $p = 0.000$; **Figure 9**).

DISCUSSION

The results of the present study demonstrate that after comprehensive rehabilitation, including BCI training, there were significant clinical improvements in UL function of subacute stroke patients. The improved clinical scores significantly surpassed routine training.

In addition to comparing with CG, we also focus on MCID. As for patients with subacute stroke, the MCID of FMA-UL is 9–10 (28). There are no MCID results for ARAT and WMFT in the subacute stage of stroke. In this study, the improvement of FMA-UL of BG not only significantly higher than that of CG, but also surpass MCID. Therefore, we concluded that clinical effect of comprehensive rehabilitation including BCI training is better than routine training. It is worth noting that the concept of MCID does not specify study duration. The clinical effect of the routine training may take longer time to manifest. The advantages of BCI training needs further observation.

Similar to the study of (45) of stroke patients with a TSS of 6 weeks to 6 months, comparison of BCI-monitored MI practice and training showed better FMA score in the BG. These results demonstrate the rehabilitative potential of BCI, which contributes to significantly better motor functional outcomes in subacute stroke patients with UL motor impairments.

The definition of "subacute" was limited to within 1–6 months after onset in consideration of the influence of spontaneous recovery (46) and relatively stable blood flow (47). In this stage, patients were able to receive more intensive training, i.e., 2–3 h per day.

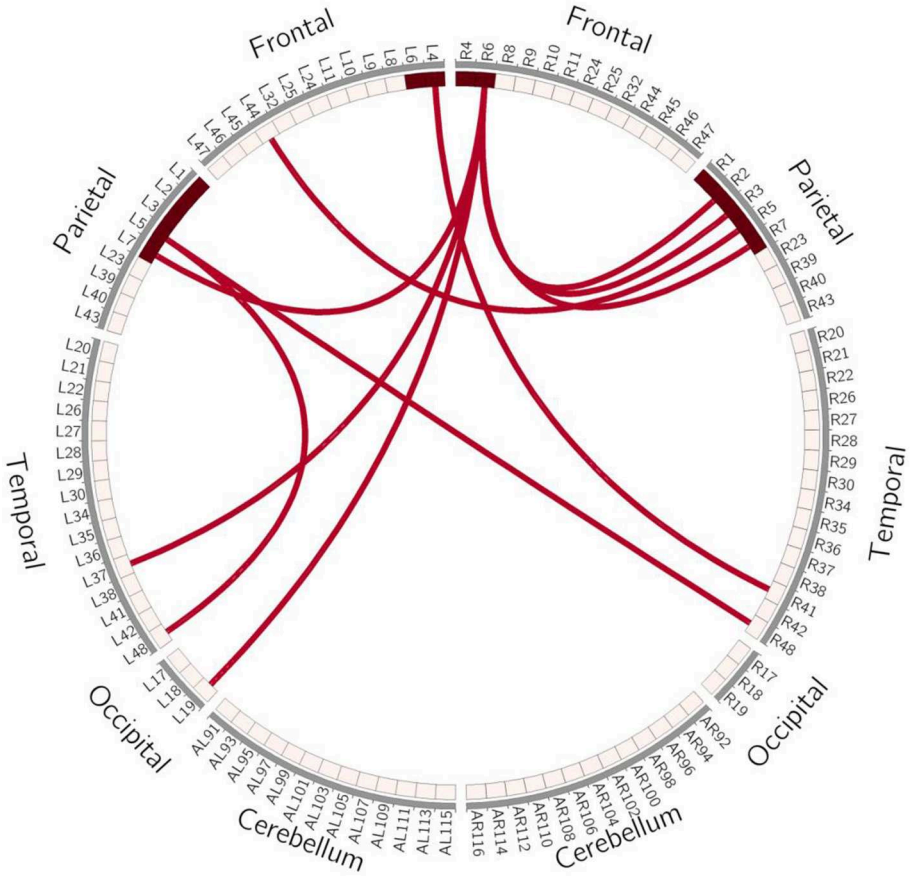

FIGURE 5 | Schematic Diagram of Increased FC in the BG. Red lines represent significantly increased inter- and intra-hemispheric FCs, L, left hemisphere; R, right hemisphere.

Concomitant rs-MRI data and correlation with measures of clinical improvement of the BG suggested possible mechanisms underlying these changes. The inter- and intra-hemispheric FCs between multiple brain regions were significantly enhanced and involved typical motor-related regions, such as the primary and premotor cortices. Moreover, we observed changes to atypical motor-unrelated regions, such as the visuospatial, visual, sensory, and somatosensory regions, as well as the primary auditory cortex. These changes may be expected to arise from the nature of BCI training. However, only FC between the somatosensory association cortex and the putamen were specifically associated with clinical improvements after BCI training. These results suggest that the extrapyramidal system may play an important role in hand control and functional recovery, with the help of sensory input.

MI-based BCI can be viewed as a special form of "motor behavior," which activates areas associated with the selection of actions and multi-sensory integration, including the premotor cortex, anterior cingulum, and parts of the superior and inferior parietal cortices (48). Our findings suggest similar increased activities among these regions. Among these areas, the premotor cortex is considered a key node, since most increased FCs are connected with it, and plays a role in direct control of certain behaviors, such as planning, as well as spatial and sensory guidance of movement, with neurons show responsiveness to stimulation of tactile, vision, and audition. It also participates in learning processes by associating sensory stimulation with specific movements or learning rules (49).

Our results indicate that the premotor cortex seemed to be crucial for the coordination and concentrate variety of functions. During BCI training, patients were required to concentrate on a video of hand movements using different tools and then to repeat these movements using mental imagery. The close relationships observed between visual and motor system was characteristic of BCI training, and was consistent with known neurofeedback dynamics occurring in the brains of patients following stroke (50). The abundance of visual signals activated the primary visual cortex (BA19), while activation of the lateral occipitotemporal cortex (part of BA37) was likely related to hand-specific visual processing. In addition, the superior parietal lobule, part of BA7, which is involved in locating objects in space and in visuo-motor coordination, serves as a point of convergence between vision and proprioception in order to determine where objects are in relation to parts of the body (51). Sensory input from the UL may also play an important role in BCI training, since training involved

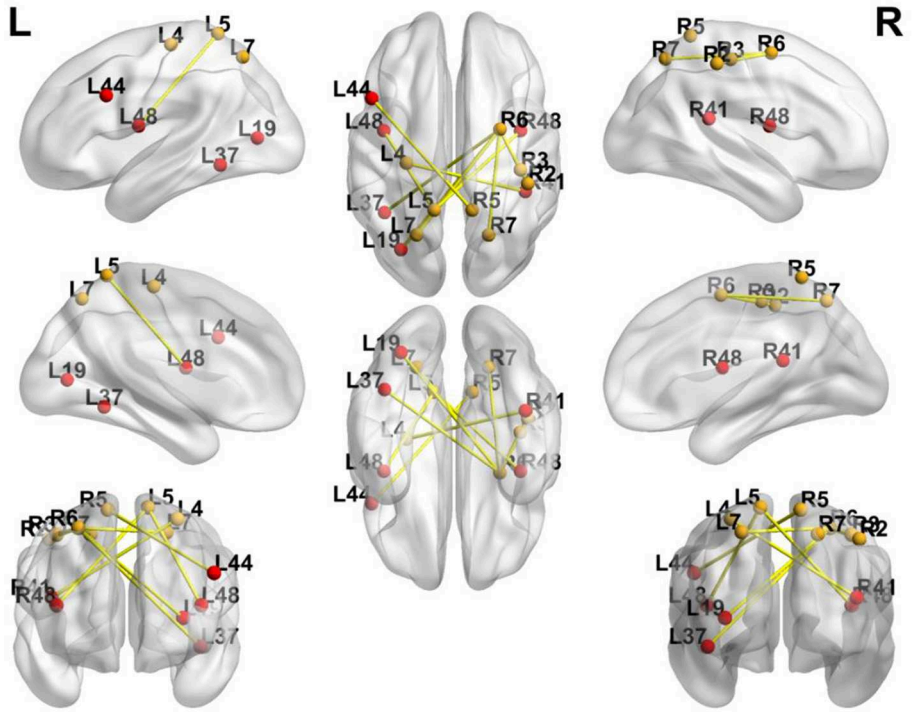

FIGURE 6 | Significance of FC Changes in the BG. Red points and yellow points indicate the significance of FC change in the BG. BA2, BA3, primary somatosensory cortex; BA4, primary motor cortex; BA5, somatosensory association cortex; BA6, Premotor Cortex; BA7, superior parietal lobule; BA41, Primary Auditory Cortex; BA37, lateral occipitotemporal cortex; BA19, associative visual cortex; BA48, putamen; BA44, pars opercularis.

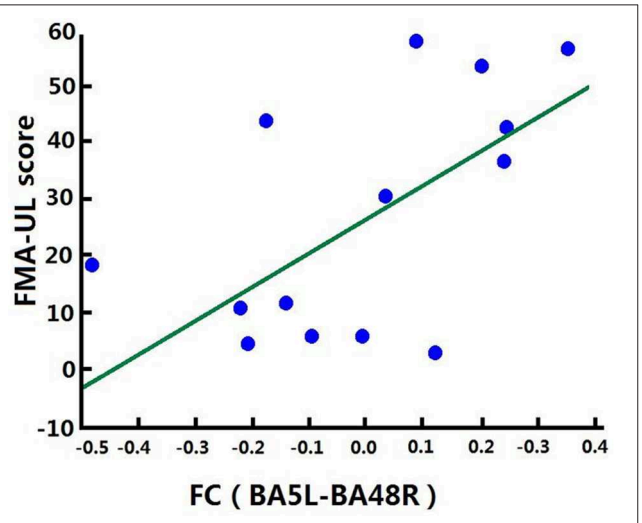

FIGURE 7 | Correlation between FC and FMA-UL$_{post}$ score of the BG. Increases in FC between the left BA5 and the right BA48 were positively correlated with FMA-UL$_{post}$ score after training in the BG. FC (BA5L-BA48R): FC between the left somatosensory association cortex and the right putamen.

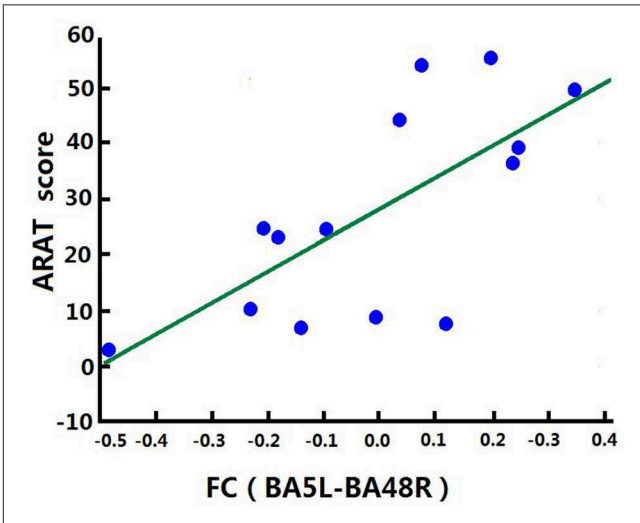

FIGURE 8 | Correlation between FC and ARAT$_{post}$ score of the BG. Increases in FC between the left BA5 and the right BA48 were positively correlated with ARAT$_{post}$ score after training in the BG.

continuous movements of the exoskeleton and routine training. Those movements likely led to the increased FC between the primary somatosensory cortex (BA2, BA3) and premotor cortex, as they relate to perception, feedback, and accurate modeling of MI. Comprehensive rehabilitation, including BCI training, can be considered as "enriched environment" training, as it integrates visual, auditory, sensory, and cognitive information simultaneously to promote functional recovery.

Outside of the typical motor-related network, we observed atypical sensory-motor integration after training. BA4,

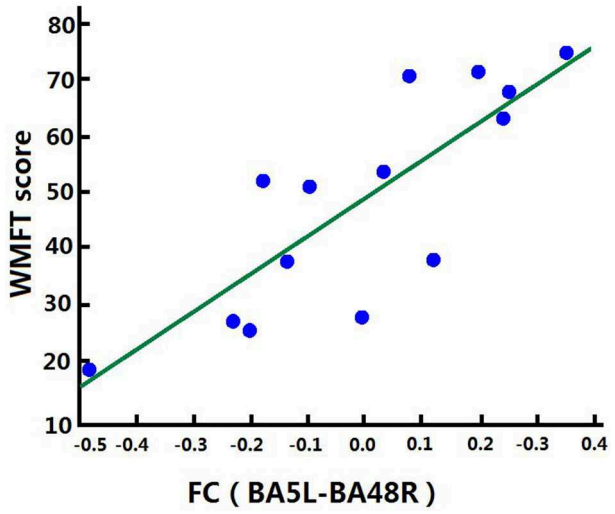

FIGURE 9 | Correlation between FC and $WMFT_{post}$ score of the BG. Increases in FC between the left BA5 and the right BA48 were positively correlated with $WMFT_{post}$ score after training in the BG.

corresponding to the primary motor cortex, is the primary region of the motor system, which works together with other systems to execute movements. Previous research indicates that BA4 also plays a key role in the early stages of motor learning and may be involved in the transition from early motor memory to long-term motor memory (52). During BCI training, patients maintained relatively constant accuracy over sessions as the task difficulty gradually increased, which supports the hypothesis that BCI training promotes an adaptive learning process. BA41 is part of the superior temporal gyrus, well-known as the auditory cortex, and is involved in a network of maintaining perceptual representations during memory-based tasks and perceptual decision-making. In an auditory discrimination task using both positive and negative reinforcement, BA41 was found to be not only responsive to reward, but also to avoidance of punishment during feedback presentation (53). In the present study, patients received two auditory signals during training, the first being a pre-warning prior to the onset of movement on the screen, and the second being feedback regarding accuracy after the movement. The auditory stimulus in this context is different from language or music. For musicians, the modulation of auditory-motor networks occurs mainly between the premotor area and the auditory cortex (54). In this study, the auditory stimulus functioned as a form of conduct training. Once familiarized, the patients did not need to distinguish the auditory stimulus, thus it shifted as an auditory signal that assisted in making an executive decision.

Beyond the premotor cortex, there were also FC changes between the somatosensory association cortex (BA5) and extrapyramidal regions. The pars opercularis (BA44) is part of Broca's area, which has non-language related functions, such as the formation of complex hand movements, associative sensorimotor learning, and sensorimotor integration (55). The observed increased FC between the somatosensory association cortex and the pars opercularis may be due to its involvement in perception and sensory feedback in complex hand movements.

In this study, only one increased FC between BA48 and BA5 was related to all clinical assessments after training, indicating the importance of the extra-vertebral system and sensory integration during the recovery of motor function. The extra-vertebral system is another important channel involved in motor control in charge of reward-based learning. BA48 is overlapped with the putamen, in the striatum. The putamen is an important integrative interface between visualization and motor intention during the process of mental rotation, which allows smooth and accurate rotation. Anatomically, the putamen forms a sensory-motor cognitive loop, which is connected to the motor cortices and the somatosensory cortex. Functionally, the putamen has been shown to be involved during the initiation of unskilled movements that require high levels of cognitive control, as well as the automatic processing of well-learned automated hand movements (56). The combination of sensory signals may help to complete the imagined spatial rotation of the hand. More importantly, the accuracy and smoothness of hand movements serve as further positive feedback for functional improvement. Therefore, enhanced FC between BA5 and BA48 can be thought of being related to clinical improvement in UL function after BCI training.

There are several features that distinguish this study from previous reports. First, few previous studies have focused on FC changes of subacute stroke patients who received BCI training. However, during the subacute phase, patients have greater potential than in the chronic phase. This study is critical for further understanding of the neural plasticity mechanisms of motor function recovery, which will improve the effectiveness of present therapies. Second, in our FC analysis, we chose direction-time correlated original values instead of absolute values, because the former more accurately represents functional motor changes after training. Additionally, we analyzed FC by combining a hemispheric Brodmann template and an AAL template for the brain stem and cerebellum, respectively, to allow a more integrated analysis of neural plasticity. Although the cerebellum plays an important role in fast and skilled movements and working memory, there was no increase in FC between the cerebellum and ROIs in this study. On the other hand, in a similar study of subacute and chronic patients, increased FC between the cerebellum and motor cortex was correlated with improved UL function after BCI training (19). The difference in these results may be related to the original values used in this study.

This study had several limitations. First, although we compared clinical improvements of comprehensive rehabilitation, which included BCI and routine training, the characteristics of spontaneous recovery on neuroimaging were not eliminated. Second, a large number of patients had weakened FCs, which may be related to clinical changes. However, the weakened FCs showed significant chaos and heterogeneity. To avoid mass data dilution, only increased FCs assessed in this study. Third, the lesions were located in different hemispheres and corresponding vessels in this study. Since there might be significant differences in the recovery patterns between hemispheres and affected areas, further

analyses of lesion position, neuroplasticity and clinical effect are crucial.

In conclusion, this study compared clinical improvements of comprehensive rehabilitation, including BCI training and routine training, and described the region and network topology alterations in subacute stroke patients following BCI training. We found that subacute stroke patients after BCI training not only showed better motor recovery, but also activities in other brain networks, including somatosensory, visual spatial processing, and motor learning. The extra-vertebral system may be involved in the improvement of motor function. Our findings suggest that after comprehensive rehabilitation, including BCI training, there was reorganization of brain functional networks topology in subacute stroke patients, thereby allowing increased coordination between multi-sensory and motor related cortex and the extrapyramidal system. We hope that this paper would give rise to more innovations to tackle the potential pathway of neurorehabilitation intervention. Future long-term, longitudinal, controlled neuroimaging studies are needed to identify the effectiveness of BCI training and approaches to promote brain plasticity in the subacute stage of stroke.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of the Beijing Tsinghua Changgung Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

QW, YP, WD, and JW designed the study. DM, HY, GL, ZY, and HZ performed experiments. WD and YG analyzed data. QW and ZY wrote the paper. All authors reviewed and approved the final version of the manuscript.

FUNDING

This study was supported by Beijing Municipal Natural Science Foundation: Key Technology Research on Ankle Rehabilitation Robot for Motor Nerve Pathways Reconstruction based on Multimodality Information Feedback (L182028), and Beijing Municipal Science and Technology Commission: Research on Rehabilitation Robot for Winter Olympic Ice and Snow Sports Injury (Z181100003118004). No additional external funding was received for this study. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

ACKNOWLEDGMENTS

We would like to thank Zhuozheng Zhao from the Department of Radiology, Beijing Tsinghua Changgung Hospital, for fMRI technical guidance and support, and all the patients for participating in this experiment. We thank International Science Editing (http://www.internationalscienceediting.com) for editing this manuscript.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

ORIGINAL RESEARCH
published: 26 February 2020
doi: 10.3389/fneur.2020.00135

Balance Testing in Multiple Sclerosis—Improving Neurological Assessment With Static Posturography?

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Background: Balance problems can severely limit the quality of life for people with Multiple Sclerosis (pwMS) already in the early stages of the disease. PwMS are usually assessed with the Expanded Disability Status Scale (EDSS), which includes a Romberg test for assessing balance. As the EDSS assessments are subjective to the examining neurologist, the postural stability of pwMS could be objectively quantified by implementing static posturography to detect balance problems and address preventive medical care.

Methods: In this cross-sectional study, we added static posturography to the neurological EDSS examination in pwMS and healthy subjects to determine how this technique could supply additional information during the evaluation of the cerebellar functional system of the neurostatus EDSS as clinical outcome already in early disease stages. Static posturography was performed with subjects standing on a force platform while outcome variables such as delineated area, average speed and average sway were obtained. Unpaired *t*-test as well as (Welch's) analysis of variance (ANOVA) with pairwise *post-hoc* comparisons according to Games-Howell were used. Spearman rank correlations were implemented to study associations of balance outcomes with EDSS-associated outcomes.

Results: A total of 99 pwMS (mean age: 35.01 years; EDSS median: 2.0, 68.69% females) and 30 healthy subjects (mean age: 34.03 years; 70% females) were enrolled. PwMS had worse performances in the three evaluated balance parameters than the healthy group (all $p < 0.001$). Even patients without postural instability as documented in the Romberg test score of the EDSS assessment showed significantly worse outcome regarding the delineated area [+1.97 cm^2, 95%-CI (0.61–3.34); $p = 0.002$] vs. healthy controls. Similar results were observed for the comparison between pwMS with normal cerebellar function EDSS-systems and healthy subjects. There were significant correlations with the EDSS, cerebellar function score and Romberg test for the delineated area and average speed (*r*'s ranging from 0.330 to 0.537, $p < 0.001$).

OPEN ACCESS

Edited by:
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Reviewed by:
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Specialty section:
This article was submitted to Neurorehabilitation, a section of the journal Frontiers in Neurology

Received: *12 December 2019*
Accepted: *06 February 2020*
Published: *26 February 2020*

Citation:
Inojosa H, Schriefer D, Klöditz A, Trentzsch K and Ziemssen T (2020) Balance Testing in Multiple Sclerosis—Improving Neurological Assessment With Static Posturography? Front. Neurol. 11:135. doi: 10.3389/fneur.2020.00135

Conclusions: Static posturography can complement neurological assessment of EDSS as an objective and quantitative test, especially for MS patients in early stages of the disease.

Keywords: balance, multiple sclerosis, static posturography, expanded disability status scale, sensitivity, Romberg test

INTRODUCTION

Multiple sclerosis (MS) is a chronic inflammatory immune disease well-known due to the heterogeneity of its clinical manifestations (1). Among them, deficits in balance are often present even in early stages of MS. In later disease stages, they are the primary cause of falling associated with further injuries (2–5). Balance itself is defined as the ability of maintaining the body center of gravity with minimal sway (6). Up to two thirds of MS patients report incapacitating balance or coordination problems in their daily life (7).

While it was initially assumed that lesions in the cerebellum were the main cause of gait and postural instability (8), it is now considered that a slowed transmission of somatic sensory impulses may have an important effect on the postural stability of MS patients (7, 9–11). A combination of central and peripheral components with afferent and efferent signals modulates the balance (7, 12). Limitation of the sensitive receptor function of muscle spindles, Golgi organs or joints is as important as the impulse transmission via peripheral nerves to the spinal cord (13, 14).

Fear of falling and its consequences dramatically limit MS patients' quality of life and can often lead to reduced activity levels, decreased productivity and social withdrawal (5, 7, 15). The inability to appropriately organize sensory information can lead to an exacerbation of impairments and to a certain selection of movement strategies to compensate for these deficits (4, 15). It is therefore of special interest to promptly identify balance dysfunction in MS patients, so appropriate medication, physiotherapy or rehabilitation strategies can be formally prescribed to minimize disability (7, 16, 17).

Currently, the examination of MS patients is supported by different neurological tests and scales (18, 19). The most used disability scale in MS is the Expanded Disability Status Scale (EDSS). This scale is well-established among neurologists, although it has been widely criticized due to its psychometric characteristics, including a poor reliability or responsiveness (18, 19). The subjective assessment of certain functional domains, especially those with barely perceptible clinical signs or low disability, may make the characterization of MS patients difficult. As part of the EDSS, a complete neurological examination is performed. The evaluation of the cerebellar functional system of EDSS includes the Romberg test, which provides orientation on pathology in the proprioceptive pathway, especially in the dorsal columns of the spinal cord (4). It can be carried out with both open and closed eyes. Approximately 10 to 20 s after closing the eyes, there is a physiological increase in swaying. A stable standing position shows that at least two of the three postural control inputs are intact (20). Limited postural control is manifested by an increase in the patient's swaying perceptible to the examiner. If an increase in swaying occurs only during absence of visual stabilization mechanisms, the pathology is suspected to be in the proprioceptive system of the body (20–22). A pathological result is however not specific for multiple sclerosis and occurs in several neurological diseases (e.g., diabetic polyneuropathy, vitamin B_{12}-deficit or alcohol-intoxication) (20).

Currently, this postural instability has to be subjectively rated by the neurologist and documented with the cerebellar functional score of the EDSS. Nevertheless, the Romberg test can be quantified and further evaluated using specialized technology to obtain quantitative and objective results. Examples are static and dynamic posturography using force platforms (7).

There have been numerous successful attempts to assess postural instability in MS patients (12, 23, 24), some of them to determine risk of falling (25–27) or to establish correlation with disease disability (26–29). A better sensitivity for static posturography than the classical Romberg test has been previously reported, even with a possible prognostic value (24). However, despite intensive research, a standardized measurement algorithm has not been established yet. Static posturography involves the electronic evaluation of the body's center of pressure or gravity, recording a wide range of more than 100 balance-relevant parameters including speed, sway, root mean square distance, delineated area or 95% confidence ellipse as well as other values (7). Even though the choice of the ideal static posturography outcome measure could be problematic due to the immense amount of available variables (30), static outcomes equivalent to delineated area, average sway and average speed of sway calculated from mediolateral sway amplitude have been shown to be the strongest predictors to discriminate impaired people with MS from healthy subjects according to the results of a machine learning approach (25).

In this study, we aimed to assess how static posturography techniques could quantify balance dysfunction in MS patients and add quantitative objective information to the EDSS. Different parameters of static posturography were compared in MS patients and healthy subjects. In addition, these parameters were put into context to the Romberg test performed as part of the EDSS Neurostatus (31).

We hypothesized that MS patients, even those with low or no clinically detected disability, would have worse performance in balance parameters than healthy subjects. The aim is to add static posturography as an objective functional test to the neurological EDSS assessment in the early stages of MS (EDSS range < 4).

METHODS

We conducted a cross-sectional study in the Multiple Sclerosis Center at the Center of Clinical Neuroscience at the Department

of Neurology, University Hospital Carl Gustav Carus, Dresden, Germany. Patients with MS (PwMS) and healthy subjects (HS) without neurological disease were invited to participate. Inclusion criteria were as follows: (1) confirmed diagnosis of Multiple Sclerosis, (2) EDSS Score between 0 and 5.0, (3) age between 18 and 50 years, (4) no acute attacks or cortisone treatment in the preceding 3 months period and (5) written informed consent. Each participant was examined according to good clinical practice (GCP) guidelines. The study was approved by the local ethics committee.

EDSS Neurostatus

PwMS underwent a full neurological examination by Neurostatus-qualified neurologists from our MS center in Dresden to calculate EDSS scores and to exclude proprioceptive or orthopedic impairment. Only patients with unrestricted ambulation and fully ambulatory patients, according to neurostatus scoring definitions, were enrolled (32).

As part of the examination, all seven functional systems and ambulation were evaluated. An important comparator of this study was the cerebellar functional system with focus on the Romberg test. The rating of the whole cerebellar functional system ranges from 0 (normal examination) to 5 (unable to perform coordinated movements due to ataxia), with 1 step intervals. Similarly, the Romberg Test is scored with 0 (normal), 1 (mild), 2 (moderate), and 3 (severe) as instructed by the neurostatus training material.

For further evaluation, PwMS were classified into three EDSS subgroups to assess the association between the degree of balance dysfunction and disability documented by EDSS. According to neurostatus scoring guidelines, patients with an EDSS step of 0–1.5 have no clinical disability with or without minimal signs of the disease. By EDSS step 2.0–2.5, minimal disability can be observed in up to two functional systems. With EDSS Step scores $\geq$ 3.0, a higher degree of disability and impact on daily activities are present.

Static Posturography

The static posturography examination was performed by a computer-driven coordination and balance analysis device that is suited for clinical use (Force Platform GK-1000, MediBalance Pro Test- and Trainingssystem, MediTECH Electronic GmbH). This platform has four piezoelectric sensors installed which measure the position of the patient's center of gravity and its variations converting pressure in electric impulses. A PC with a software package included with the Force Platform was connected to the platform, including a diagnosis software with multiple measurement capabilities. With electronic amplification, coordinates for the center of gravity were automatically calculated on a two-dimensional plane (33).

A trained individual gave proper instructions to the subjects for a standardized assessment and was not privy to the disease diagnosis. To assess the subject's balance, static posturography was performed using the Romberg test's position. Subjects were asked to stay upright and barefoot on a corresponding marked area upon the measurement platform as stable as possible. Patients stood with a standardized position with their feet separated using a track width of 10 cm and with horizontally raised arms in front of them with palms facing up as a provocation and distraction mechanism (20). Each measurement was started after a sufficient adjustment period of 20 s standing on the electronic platform with closed eyes and had a duration of 30 s. Measurements were performed with closed eyes to emulate the balance conditions adopted by the patients during the evaluation of the Romberg Test as part of the cerebellar function system score of the EDSS. Retiring visual stimulation may uncover masked proprioception or sensory disorders that may be present within pwMS (20).

Balance Outcomes

The balance parameters assessed by static posturography were defined as follows:

- Delineated area: described surface during the measurement of the center of gravity of the subject. Continuous triangles from the mean value of all measurement values of the last point to the current measurement point are calculated (>95% confidence interval). Points on the grid which overlap numerous times are not counted more than once (measured in mm^2).
- Average sway: average distance of all measurements from the center of all measurements (in mm).
- Average speed: average speed at which the central pressure point of the subjects moves on the platform (measured in mm/s).

These outcome measures were automatically generated by the commercially distributed Force Platform GK-1000 as mediolateral sway measures.

Statistical Analysis

Normality of data was assessed visually using quantile-quantile plots and confirmed with Shapiro–Wilk tests. Parametric analyses were used, unless otherwise stated. To stabilize variance and to optimize normality for (slightly) right-skewed distributions of balance outcomes, balance variables were log transformed before analyses. Quantitative population characteristics were presented as measures of central tendency (mean, median), followed by standard deviation (SD). Categorical characteristics were expressed as relative frequencies. In the evaluation of balance parameters, a descriptive specification of (crude) mean values and standard deviations occurred. Comparisons between MS patients and healthy subjects were made with unpaired *t*-test and Chi-squared tests, accordingly. To evaluate mean differences between population subgroups (healthy subjects and patient subgroups according to EDSS, Cerebellar FS or Romberg test), variance of analysis (ANOVA) was carried out. In case of not achieving variance equality (as indicated by Levene's test), Welch's ANOVA was used. In case of statistically significant ANOVA results, Games-Howell *post-hoc* test was conducted to compare means of subgroups pairwise, as Games-Howell does not assume equal sample sizes (nor variances). Spearman rank correlations were calculated to study bivariate relations of balance outcomes with EDSS, Cerebellar FS and Romberg Test results. Significant results were those with (adjusted) significance levels of $p < 0.05$. All statistical analyses were performed using IBM SPSS version 25.0 (IBM Corporation, Armonk, NY, USA).

TABLE 1 | Balance parameters in healthy subjects and PwMS.

	Healthy ($N = 30$)		PwMS ($N = 99$)		
Balance parameters	**Mean**	**Standard deviation**	**Mean**	**Standard deviation**	***p***
Delineated area (cm^2)	1.67	0.98	5.48	7.65	<0.001
Average sway (mm)	12.94	6.75	16.04	7.59	0.039
Average speed (mm/s)	16.22	3.97	24.40	14.66	<0.001

RESULTS

A total of 129 study participants (mean age 34.78; 69% female; 99 PwMS and 30 corresponding HS) were examined. The mean age of the PwMS group was 35.01 years (SD 8.21), 68.7% were female, with a median EDSS of 2.0 on a range from 1.0 to 5.0. The average time since MS diagnosis was 5.5 years (SD 4.62). No patient presented an EDSS score of 0. The HS group presented a mean age of 34.03 (SD 7.99) years with 70% of female gender. Both groups differed neither in age ($p = 0.893$) nor in gender ratio ($p = 0.563$).

Cerebellar Function Score in Neurostatus EDSS Examination Including Romberg Test

PwMS had a mean cerebellar function score of 0.74 (SD 0.78; median 0), ranging from 0 to 3; 42.42% of patients had a normal cerebellar function (with a score of 0), 41.4% of 1, 12.1% of 2, and 4% of 3. For the Romberg test, the mean score was 0.32 (SD 0.55; median 1), with scores between 0 and 2 points (71.7% had a score of 0, 24.2% of 1 and 4% of 2).

Static Posturography in MS Patients and Healthy Subjects

Table 1 shows the static posturography results of MS patients and healthy subjects. Significant differences between both groups could be observed in the three evaluated parameters, namely: delineated area pwMS vs. HS (5.48 cm^2, SD 7.65 vs. 1.67 cm2, SD 0.98; $p < 0.001$), average sway (16.04 mm, SD 7.59 vs. 12.94 mm, SD 6.75; $p = 0.047$) and average speed (24.40 mm/s, SD 14.66 vs. 16.22 mm/s, SD 3.97; $p < 0.001$).

Balance Parameters According to EDSS Step Score

The balance parameters were also analyzed according to EDSS subgroups. Subgroup EDSS 3.0–5.0 differed in all three outcome parameters from the healthy group (**Table 2**). Further, for delineated area and average speed, the subgroups EDSS 2.0–2.5 and EDSS 0–1.5 also differed from the healthy group, whereas average sway difference from these subgroups did not reach statistical significance.

Patients with an EDSSscore between 0 and 1.5 showed significant differences to the healthy group regarding the delineated area (+1.79 cm^2, $p = 0.01$) and average speed (+5.17 mm/s, $p = 0.007$) (**Table 2**).

The correlation coefficients with the EDSS were significant for all three balance parameters. The delineated area showed the strongest correlation according to Spearman with $r = 0.427$ ($p < 0.001$) (**Table 3**). The parameters delineated area and average speed had a very strong correlation ($r = 0.817$, $p < 0.001$).

Balance Parameters According to Cerebellar Function Score and Romberg Test

Considering just the cerebellar functional system of the EDSS, the delineated area and the average speed differed between HS and pwMS subgroups $F_{(3,123)} = 11.16$, $p < 0.001$ and $F_{(3,123)} = 11.97$, $p < 0.001$, respectively. Games-Howell *post-hoc* analysis revealed a significant difference between HS and pwMS, with a cerebellar score of 0 in the delineated area (+0.519 cm^2, $p = 0.032$) (**Figure 1**). This parameter and the average speed of sway could differentiate pwMS with a cerebellar score of 1 from HS as well ($p < 0.001$) (**Figure 1**).

Similarly, the delineated area and average speed could differentiate pwMS according to Romberg test score and HS, namely $F_{(3,125)} = 10.08$, $p < 0.001$ and $F_{(3,125)} = 10.86$ $p < 0.001$, respectively. Additionally, HS differed from pwMS with a Romberg test score of 0 in delineated area (+0.56 cm^2, $p < 0.001$) and average speed (+0.200 mm/s, $p = 0.008$) (**Figure 2**). The mentioned parameter, as well as the average speed could also differentiate HS from MS patients with a Romberg score of 1 ($p < 0.001$).

Both delineated area and average speed were also significantly correlated to the cerebellar function system score and Romberg test ($p < 0.001$) (**Table 3**).

Patients With Normal Cerebellar Function and Romberg Tests and Impaired Balance Parameters

An additional analysis was performed to detect the number of pwMS with normal cerebellar function system score and Romberg tests that had impaired balance parameters compared to HS. Three cut-points were evaluated. Considering a strict limit of 3 standard deviations from the healthy group, 21.43% (9 out of 42) of pwMS with a normal cerebellar function score according to the neurologist had an impaired delineated area and 19.05% had an impaired average speed of sway (**Table 4**).

Similar results can be seen regarding the Romberg test score. Among those with a score of 0, up to 39.44% (28 out of 71) had an impaired delineated area and 26.76% an altered average speed of sway with a limit of 3 SD from the healthy group. A great proportion of patients had still impaired values considering stricter limits (**Table 4**).

DISCUSSION

In this study, we were able to analyze different balance parameters in healthy subjects and patients with different disability degrees. Our MS group was typical for MS patients

TABLE 2 | Balance parameters in healthy subjects and MS patients according to EDSS Step Score.

Groups (*N*)	Healthy (*N* = 30)		EDSS 0–1.5 (*N* = 40)		EDSS 2.0–2.5 (*N* = 30)		EDSS 3.0–5.0 (*N* = 29)		
Balance parameters	**Mean**	**Standard deviation**	**Mean**	**Standard deviation**	**Mean**	**Standard deviation**	**Mean**	**Standard deviation**	***p* (ANOVA)**
Delineated Area (cm^2)	1.67[b,c,d]	0.98	3.46[a,d]	4.07	4.00[a]	2.86	9.79[a,b]	12.09	<0.001
Average Sway (mm)	12.94[d]	6.75	14.11	7.20	15.64	6.06	19.11[a]	8.72	0.025
Average Speed (mm/s)	16.22[b,c,d]	3.97	21.39[a,d]	10.65	20.96[a,d]	7.83	32.12[a,b,c]	21.06	<0.001

[a]*significant difference with healthy group ($p < 0.05$) in post-hoc analysis.*
[b]*significant difference with EDSS 0–1.5 group ($p < 0.05$) in post-hoc analysis.*
[c]*significant difference with EDSS 2–2.5 group ($p < 0.05$) in post-hoc analysis.*
[d]*significant difference with EDSS 2.5–3.0 group ($p < 0.05$) in post-hoc analysis.*

TABLE 3 | Correlation coefficients between balance parameters and EDSS step scores, cerebellar function system and romberg test in MS patients (*N* = 99) according to spearman.

	EDSS step score	Cerebellar function system	Romberg test
Delineated area	$r = 0.427$ ($p < 0.001$)	$r = 0.404$ ($p < 0.001$)	$r = 0{,}537$ ($p < 0.001$)
Average sway	$r = 0.330$ ($p < 0.001$)	$r = 0.131$ ($p = 0.201$)	$r = 0.153$ ($p = 0.131$)
Average speed	$r = 0.334$ ($p < 0.001$)	$r = 0.349$ ($p < 0.001$)	$r = 0.431$ ($p < 0.001$)

considering age and sex ratio. We characterized our study population with the most used clinical scoring scale in MS (EDSS), including its cerebellar function system score and the Romberg test. With static posturography, balance impairment could be detected even in patients without disability according to the neurological examination.

The first hints of subtle changes in postural stability came from a study by Karst et al., which confirmed the suitability of posturographic processes for long-term observation of standing stability in only slightly impaired MS patients (34).

As expected, as the neurological disability increases, the postural balance is progressively impaired. Patients with higher EDSS scores needed a larger area for standing than healthy subjects or patients with a lower score, confirming previous reports that postulated growing standing instability with an increase in the severity of clinical impairment (4, 23, 26–28).

Our study was also able to demonstrate significant differences in balance parameters between MS patients with minimal EDSS scores (1.0–1.5) and healthy subjects. These results vary slightly from previous reports, where there was no difference in patients with an EDSS score < 2.0 compared to healthy subjects (28). Further, considering just the cerebellar function system and the Romberg test, a difference in the delineated area and average speed of sway between MS patients and healthy subjects was already detected in the cerebellar function system and Romberg tests, even in those with values of 0 or 1 in these tests.

In the scoring of the EDSS, patients assessed with a 0 have no signs of clinical disease detected by the physician; those with a score of 1 may have signs only of the disease but no disability on daily activities. With static posturography, balance alterations could be detected before they were perceivable by either the physician or the patient according to the EDSS and the evaluated cerebellar function and Romberg test.

Even with the strictest cut-point definitions, up to 21.43 and 39.44% of patients had impaired delineated area values, even if a normal cerebellar function respective Romberg test was previously determined by the physician. Similar results were reported by Melillo et al., who detected balance abnormalities in several patients with normal Romberg test scores with possible prediction of balance impairment after a 1-year follow-up (24). Our results are therefore in agreement with previous publications that indicate a better sensibility of balance parameters than trained neurologists (24, 35, 36).

Additionally, the delineated area and the average speed of sway had moderate correlations with the EDSS, cerebellar function system score and Romberg test, confirming preceding findings (26, 27, 36, 37). Previous studies could even predict EDSS scores using static posturography (29).

The correlation between the delineated area and the average sway was high ($r = 0.817$). However, both were less correlated with the average sway ($r = 0.424$ and $r = 0.457$, respectively). This is in line with the results reported in our study, as the average sway had the lowest sensitivity detecting impairment between pwMS and HS. This may be a consequence of specific technical characteristics of the GK-1000 Force Platform available for this study related to the used piezoelectric sensors responsible for the measurement of the patient's center of gravity and its projection on the field. The average sway was a unidimensional outcome measure (mm) and could have a lower sensibility. The delineated area and the average sway could represent a support for physicians assessing disease impairment and addressing further therapeutic procedures, especially in patients with low or undetectable disability.

However, some limitations of our study should be considered. Firstly, different force platforms as well as different techniques for static posturography are currently available, and results could vary according to the methods used for the calculation of balance parameters. We consider the ideal solution for increasing comparability between different studies to be the use of precisely similar force platforms and extraction software. The use of commercially distributed systems could unify outcomes obtained from pwMS. Second, there are no reference values available

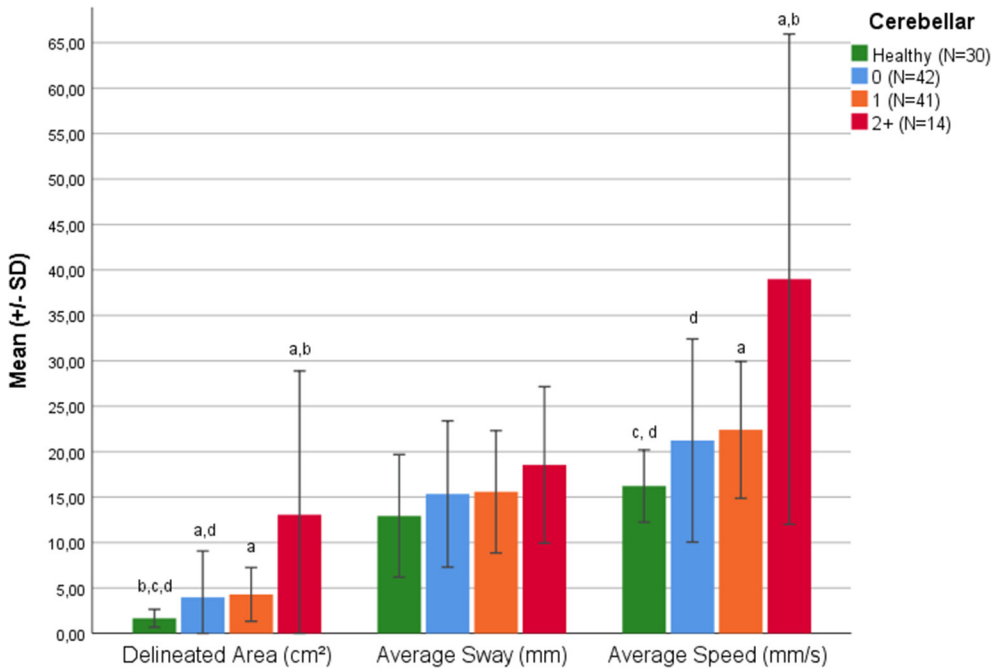

FIGURE 1 | Balance parameters in healthy subjects and in pwMS classified according to Cerebellar Function Score. a = significant difference to healthy group ($p < 0.05$). b = significant difference to Romberg Score 0 ($p < 0.05$). c = significant difference to Romberg Score 1 ($p < 0.05$). d = significant difference to Romberg Score 2+ ($p < 0.05$).

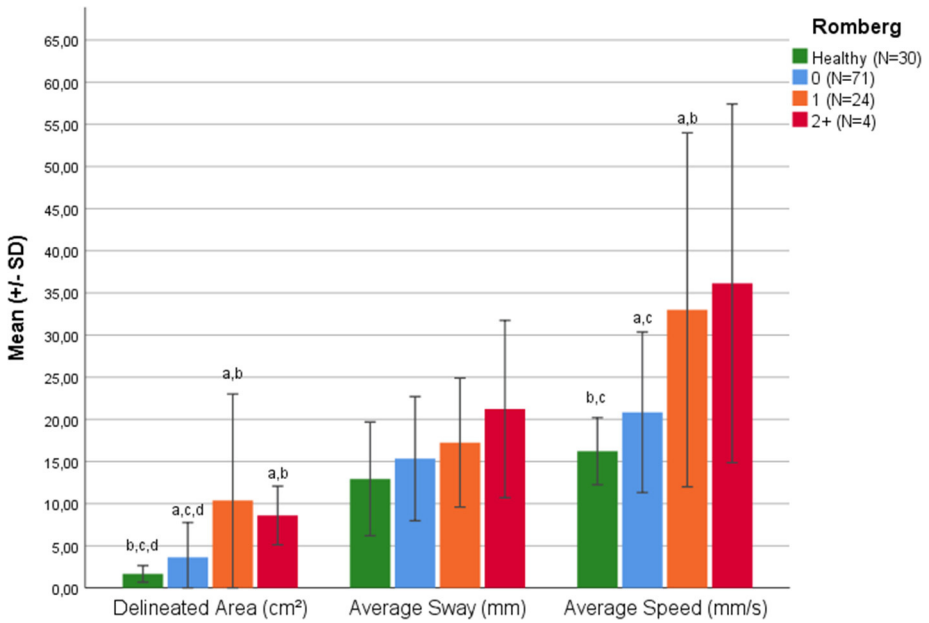

FIGURE 2 | Balance parameters in healthy subjects and pwMS classified according to Romberg Test. a = significant difference to healthy group ($p < 0.05$). b = significant difference to Cerebellar Score 0 ($p < 0.05$). c = significant difference to Cerebellar Score 1 ($p < 0.05$). d = significant difference to Cerebellar Score 2+ ($p < 0.05$).

for our used platform, which can support the detection of imbalance. We proposed the use of standard deviations from a HS group for this goal. Further analysis with more representative HS groups should be performed. However, our HS and pwMS groups showed similar age and gender ratio. Third, we conducted a cross-sectional study. Future research should focus on a longitudinal evaluation which might provide further insights into the utility and prognostic value of the used technique.

The results of our study support the use of static posturography in clinical practice. This technique could be

TABLE 4 | Patients with cerebellar function system score 0 ($N = 42$) or Romberg test score 0 ($N = 71$) with impaired balance parameters according to different cut-points for deviation from the healthy group.

		2 SD	2.5 SD	3 SD
Cerebellar function system score = 0 ($N = 42$)	Delineated area	13 (30.95%)	10 (23.81%)	9 (21.43%)
	Average sway	6 (14.29%)	2 (4.76%)	1 (2.38%)
	Average speed	10 (23.81%)	8 (19.05%)	8 (19.05%)
Romberg test score = 0 ($N = 71$)	Delineated area	39 (54.93%)	30 (42.25%)	28 (39.44%)
	Average sway	13 (18.31%)	5 (7.04%)	2 (2.82%)
	Average speed	26 (36.62%)	19 (26.76%)	19 (26.76%)

useful to address preventive strategies in patients with low disability and prevent further falls and lesions due to imbalance (26, 38, 39). Ideally, therapeutic interventions should be introduced even before postural stability deficits become clinically relevant, which is precisely why the development of reliable diagnostic procedures for the early detection of walking and standing instability is relevant in clinical practice (34). Future approaches could consider concomitant MS impairments such as cognitive dysfunction and their effect on postural control using static posturography. PwMS could be more unbalanced by adding cognitive tasks and an improvement of balance function after multi-tasking training has been reported (40–42).

All three evaluated parameters were able to differentiate pwMS from HS. Nevertheless, just the delineated area and average speed could detect differences between HS and pwMS with normal cerebellar function and Romberg test. They could therefore be used for future studies and examinations where balance is concerned.

Static posturography parameters could moreover be used as outcome measures in clinical trials, complementing the EDSS with additional advantages regarding psychometric characteristics of its execution. Results are obtained on a continuous linear scale, with better reliability as it is less operator-dependent and possibly associated with greater sensitivity compared to the EDSS.

Overall, the balance platform test seems suitable for assessing the current postural stability of MS patients. Future studies should evaluate the responsiveness or sensitivity to change, in order to determine if it could be used for the development of a standardized measurement for the middle and long-term follow-up of disease progression and for treatment response evaluation toward the digitalization and objective assessment in medicine.

CONCLUSION

Balance parameters obtained with static posturography were able to discriminate between MS patients and healthy subjects, even without disability detected by a physician using the EDSS and the Romberg test. Specifically, the delineated area and average speed of sway measured with the patient standing with eyes closed are sensitive parameters for the assessment of balance impairment in early stages of the disease. These tools could complement the EDSS and neurological examination for a more sensitive and objective assessment of MS patients.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation, to any qualified researcher.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethikkommission an der Technical University Dresden. Approval number: EK 224062011. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

HI, DS, AK, KT, and TZ contributed conception and design of the study and wrote sections of the manuscript. HI and DS organized the database and performed the statistical analysis. TZ, DS, and HI wrote the first draft of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

FUNDING

We acknowledge support by the Open Access Publication Funds of the SLUB/TU Dresden.

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Conflict of Interest: TZ received personal compensation from Biogen, Bayer, Celgene, Novartis, Roche, Sanofi, and Teva for consulting services. TZ received additional financial support for the research activities from Bayer, BAT; Biogen, Novartis, Teva, and Sanofi.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

ORIGINAL RESEARCH
published: 03 April 2020
doi: 10.3389/fneur.2020.00195

A Mindfulness-Based Stress Reduction Program via Group Video Conferencing for Adults With Cerebral Palsy – A Pilot Study

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Purpose: Adults with cerebral palsy experience challenges related to lifelong disability, such as stress, fatigue, pain and emotional issues. E-health services can be delivered regardless of residence and level of functioning. The aim of this pilot study was to explore the potential benefits and feasibility of a mindfulness-based program delivered to adults with cerebral palsy via group video conferencing.

Methods: Six adults with cerebral palsy received an 8 week mindfulness group-based program via video conferencing. A multiple single-case study design was applied, including quantitative and qualitative elements. Pain was assessed 16 times through the study period. Questionnaires were administered to gather data on pain catastrophizing, stress, fatigue, emotional distress, positive and negative affect, and quality of life. A focus group interview addressed experiences with the intervention and the mode of delivery.

Results: The participants' pain levels showed varied trajectories. Pain catastrophizing and negative affect were statistically significant decreased. Qualitative data indicated benefits from mindfulness in coping and stress management. The video conferencing delivery was evaluated as feasible, with no major adverse effects.

Conclusion: Since the pilot study had a small sample size, potential treatment benefits should be interpreted with caution. However, this pilot study provides important information in the planning of future larger and controlled studies on mindfulness-based interventions programs via video conferencing for adults with cerebral palsy and other persons living with long-term disability.

Keywords: disability, pain, stress, coping, mindfulness, e-health, cerebral palsy, adult

OPEN ACCESS

Edited by:
Marcello Moccia,
University of Naples Federico II, Italy

Reviewed by:
Catherine Mak,
University of Queensland, Australia
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Specialty section:
This article was submitted to Neurorehabilitation, a section of the journal Frontiers in Neurology

Received: *12 December 2019*
Accepted: *04 March 2020*
Published: *03 April 2020*

Citation:
Høye H, Jahnsen RB, Løvstad M, Hartveit JF, Sørli H, Tornås S and Månum G (2020) A Mindfulness-Based Stress Reduction Program via Group Video Conferencing for Adults With Cerebral Palsy – A Pilot Study. Front. Neurol. 11:195. doi: 10.3389/fneur.2020.00195

INTRODUCTION

Cerebral palsy (CP) is an umbrella term covering a group of motor impairments resulting from an early brain lesion (1). CP is often accompanied by disturbances in sensation, cognition, perception and behavior, and secondary problems in the musculoskeletal system (1). The prevalence of CP is approximately two per 1,000 births (2, 3). Many people with CP experience secondary problems

with increasing age, such as chronic pain, fatigue, and deterioration of function (4–8). As many as 28–67% of adults report chronic pain to the degree that significantly affects mastery and participation, which poses long-term stress factors to the individual (6, 7).

Follow-up programs for individuals with CP have typically had a predominant focus on development and preservation of motor skills, while somatic symptoms and psychosocial factors have been largely ignored (9). Based on a narrative review on adults with CP of factors related to mastery of their disability and health with age, their main concerns were need of social support, self-acceptance and acceptance by others, adaptations in everyday life, and health-care services related to the disability (10). By this, several studies have highlighted the need for complementary intervention programs that enhance self-regulation of physical and emotional well-being (11), counteract loneliness (12), and facilitate the coping potential of the individual (4, 9, 10). This also applies to programs that target long-term pain among persons with CP, where standard medically oriented interventions are typical (6, 7, 13). A study addressing CP-related pain, however, found that having catastrophizing thoughts about the pain negatively affected daily functioning and was associated with depression (4). Therefore, there is a need for more research on coping strategies and psychologically oriented interventions in this patient group.

The recognition of the individual's coping potential is central to the biopsychosocial model, which promotes that biological, psychological, and social factors are interactively involved in health and well-being (4, 14). Coping strategies are described as the repertoire of responses the individual has to manage thoughts, feelings, and actions in demanding and stressful situations (15, 16) The coping strategies are influenced by how the person understands and interprets the situation, perceived source of stress, locus of control, sense of self-efficacy, and by access to social support. According to Sahler and Carr (16), coping strategies can be taught explicitly or through modeling, and therefore have a potential for lifelong development. Facilitating adaptive coping for fatigue, pain, and stress associated with living with CP might therefore be an important part of holistic rehabilitation approaches to this group.

Mindfulness-based stress reduction (MBSR) is a standardized program, that aims at enhancing aspects of coping with distress (17, 18) and disability in everyday life (19, 20). MBSR trains the capacity for conscious presence in the here and now of mind and body, and to adopt a non-judgmental and accepting attitude toward emotions, thoughts, and bodily sensations. In this perspective, mindfulness can be seen to aid individuals in making a more realistic evaluation of stressors. Also, when in a mindful state, it gives the individual a potential to act more purposefully and flexibly to stressors (21, 22). Studies of mindfulness-based interventions in patient groups such as cancer, fibromyalgia, irritable bowel syndrome, and osteoarthritis patients, have shown that the approach can positively influence symptoms, including pain (23–26), fatigue (27, 28), depression, negative affect, and anxiety (29, 30). A study of a mindfulness-based intervention (MiYoga) for children with CP found significant positive effects on better-sustained attention and fewer impulsive errors, but no effects on psychological well-being, quality of life, or physical function (31). Thus, because MBSR has a wide range of positive health benefits in various patient populations, we wanted to explore the usefulness of MBSR for adults with CP.

The existing literature on VC-based interventions indicates that, when effective, the technology can contribute to improved service accessibility (32) regardless of living area and physical mobility. VC might also reduce the patients' use of time, energy, and costs (33). Thus, providing in-home interventions might be particularly beneficial for adults with CP, by increasing accessibility despite limitations in mobility. We are not aware of prior studies describing either an MBSR intervention alone or MBSR delivered by VC in adults with CP.

The main aim of this pilot study was to explore the benefits of a group- and VC-based MBSR program in adults with CP, with respect to the self-reported experience of pain, emotional distress, quality of life, and coping. A secondary aim was to evaluate the feasibility of this particular mode of service delivery, including the participants' experiences with the technical solution applied.

MATERIALS AND METHODS

Design

This pilot study applied a descriptive multiple single case design and included both quantitative and qualitative data.

Participants

The study was advertised at the Sunnaas Rehabilitation Hospital (SRH) in-patient program for adults with CP, SRH's website, and at the Norwegian CP association's website and paper magazine. Potential participants were referred from their general physicians, and assessed for eligibility by the physician and psychologist who led the MBSR intervention (authors GM and HH). Inclusion criteria were: minimum 18 years of age; with uni- or bilateral spastic CP (34) and gross motor function level (GMFCS) (35) I–IV; pain of at least 3 months with an average score last week of minimum 3 on the numerical rating scale (NRS) (36); movement of the arms and neck to a degree that allowed performance of yoga exercises; and sensory-motor and communicative skills that enabled group-participation via VC. Exclusion criteria were intellectual disability, severe ongoing mental illness and drug abuse. All participants provided written, informed consent to participate before the data collection. The study was approved by the Patient Safety Officer at SRH and by the Regional Committee for Medical Research Ethics, South-Eastern Norway (216/962). The participants have been anonymized and given pseudonyms.

Data Collection Procedures

The project was conducted at or from SRH with the participants physically attending SRH at T1 and T3 (**Figure 1**). Baseline assessments with self-reported questionnaires was performed before (T1), immediately after (T2), and 4 months after the intervention (T3). Current pain intensity was assessed weekly on the same day ($n = 1$–16) between 12 and 2 PM throughout the study period (**Figure 1**). A custom made evaluation questionnaire regarding the intervention and experience with

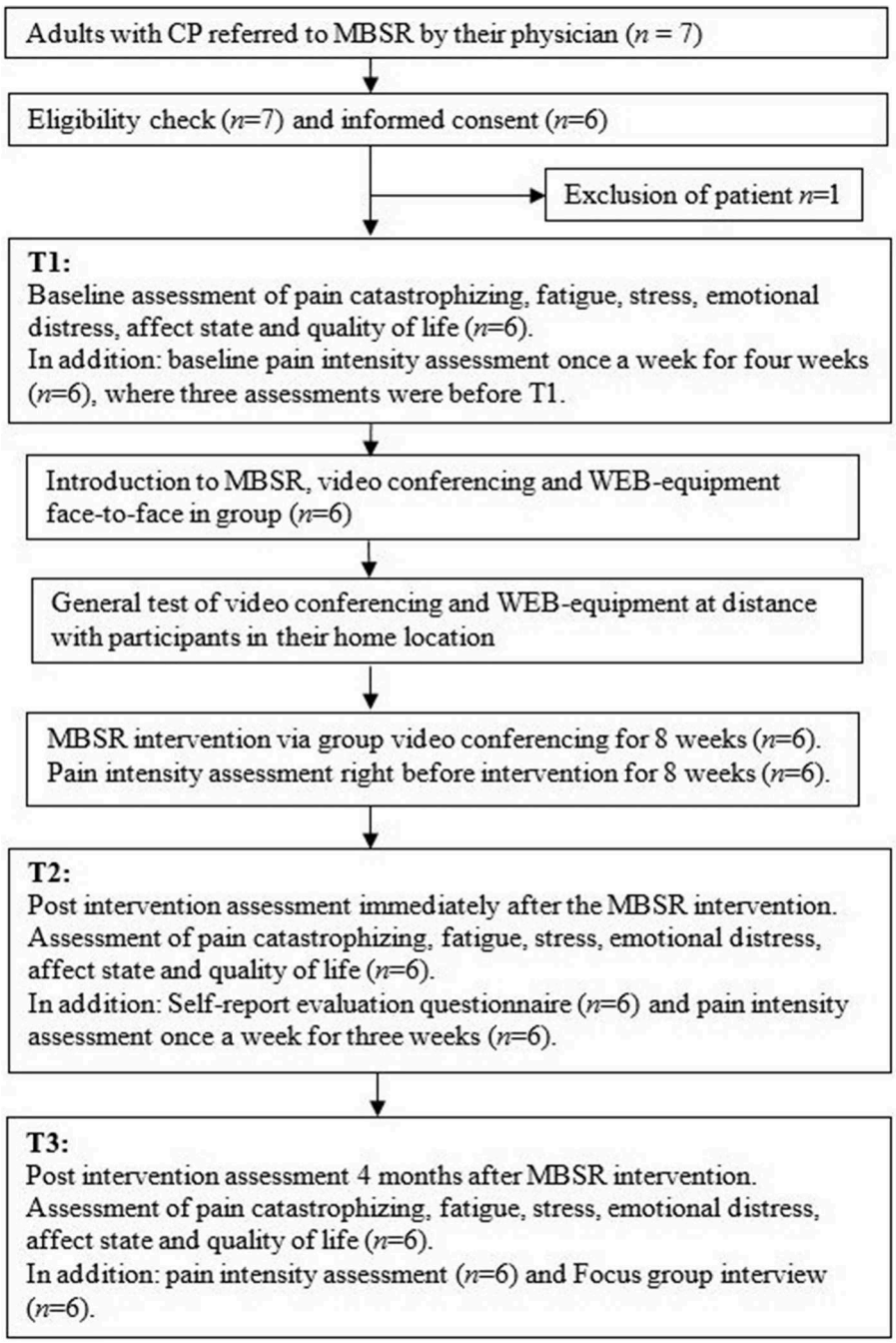

FIGURE 1 | Flow-chart for logistics during the study period.

use of VC was administered at T2. An audio-recorded focus group interview was conducted at T3 and carried out by the interventionists (authors HH and JFH), and the person responsible for technical equipment and support (author HS).

Baseline and Outcome Measures

Sample characteristics, and intervention effects were explored with the following measures:

Pain intensity was assessed on a 0–10 Numeric rating scale (NRS), where 0 is no pain, and 10 is unbearable pain. According to Breivik et al. (37), mild pain is classified as a score of 1–3, moderate pain from 4 to 6, and severe pain from 7 to 10. A score of $\geq$3 was used as a clinical cut off (37, 38).

The Pain Catastrophizing Scale (PCS) (39) assesses catastrophic thinking about pain. It consists of 13 items and is translated and validated in Norwegian. Internal consistency

assessed by Cronbach's alpha were 0.9 (40). Answers are provided on a five-point scale (0–4), with a maximum score of 52, with ≥30 considered as clinically relevant cut-off.

The Perceived Stress Scale (PSS 14) (41, 42) is a 14-item questionnaire developed to measure the degree to which situations in one's life are appraised as psychologically stressful. Cronbach's alpha of 0.76–0.78 has been reported (41). The maximum total score on the 14 items is 56. A score of ≥25 was used as clinical cut-off (43).

The Fatigue Questionnaire (FQ) (44, 45) is an 11-item questionnaire that assesses physical and mental fatigue, and also provides a total score. Internal consistencies assessed by Cronbach's alpha were 0.73 (MF), 0.86 (PF), and 0.86 (TF), respectively (45). Responses are scored on a scale from 0 to 4, and a total score of ≥16.8 (1.0 SD above normative the mean) was used as a clinical cut-off (46).

The Hospitality Anxiety and Depression Scale (HADS) (47) assesses symptoms of anxiety (HADS-A) and depression (HADS-D) in medical and psychiatric settings and the general population, and has been validated in Norway. A review showed average Cronbach's alpha of 0.82 (anxiety) and 0.83 (depression) (48). Both HADS-A and -D consist of seven questions which are scored on a scale from 0 to 3, giving a maximum score for each subscale of 21. A cut-off of ≥8 was considered as the clinical relevant cut-off for both anxiety and/or depression (48).

The Positive Affect and Negative Affect Schedule (PANAS) (49) was used to assess positive (PA) and negative (NA) affect. We used the state version, where participants are asked to indicate to what extent they experienced each of the named adjectives at the time of assessment. PANAS has good psychometric properties, with Cronbach's alpha of 0.85 (PA) and 0.90 (NA) (50). Norms from a general UK population were used [mean score for NA = 16 (SD 5.5) and mean score for PA = 31.5 8 (SD 7.65)] (46). On the basis of the UK population study, NA ≥ 21.5 (1 SD above the normative mean in the UK study), and PA ≤ 23.85 (1 SD below the normative mean in the UK study) were used as clinical cut-off (46).

The Perceived Quality of Life Scale (PQoL) (51) was used to assess the quality of life. The PQoL questionnaire consists of 19 items, where the mean score is reported, and 10 is the highest score. In a Norwegian validation study (52), the Cronbach's alpha was 0.93. From that study, the mean score in a healthy population was 7.1 (SD 1.2). A score of ≤5.9 (1.0 SD below the normative mean in the same study) was considered as clinically relevant cut-off.

The evaluation questionnaire consisted of 12 custom made questions with fixed response alternatives and spaces for open comments, asking about satisfaction with the intervention, the benefit of it in everyday life, and their experience with VC (**Table 4**). The responses were subsequently used to develop an interview guide to be used in the focus group interview. A focus group interview approach was selected because the method is suitable for incorporating a reflexive process about themes, to explore the breadth and exchange of opinions and experiences in a group, and identifying what might represent shared experiences among the participants (53, 54).

Mindfulness-Based Intervention

The introduction to MBSR was given to the group face-to-face at SRH and included training in the use of the technical equipment. After that, the participants received weekly VC-based MBSR in their homes over 8 weeks. **Table 1** describes the different themes and sessions. Participants were connected to a closed web-group on their PC, with web-camera, speakerphone, and VC software installed. They could see and hear the instructors and the other participants, ask questions, and make comments. The online sessions were conducted from SHR by the MBSR certified psychologist (author HH) and yoga certified physiotherapist (author JFH), Both authors were highly experienced with using MBSR and yoga to different patient groups in the field of neurological rehabilitation at SRH.

The MBSR program was accommodated and modified to the technological solution and the CP population in the following ways: (a) each session was shortened from 2 to 1.5 h; (b) there were no full-day retreat or instruction on writing diaries; (c) yoga exercises were performed from a sitting position; (d) information was provided on stress and pain physiology and the importance of mental factors in modulation of pain signals; and (e) topics related to fatigue and concentration were included. The participants received written summaries of each session; they were encouraged to practice formal exercises daily and received audio files with instructions of the body scan and the breathing anchor exercises.

Technology and Safety

The Unit for Technology and eHealth at SRH was responsible for the technical solutions and support. The Acano/Cisco

TABLE 1 | MBSR session overview.

- Welcome by instructors
- Participant exchange of experience (related to mindfulness and the theme from previous session)
- Formal exercise (breathing anchor, body scan, visualization exercises or yoga)
- Theme:
  - Week 1: Mindfulness: what it is and how you do it
  - Week 2: Attention and awareness: to be present
  - Week 3: Stress: responding vs. reacting
  - Week 4: Pain: responding vs. reacting
  - Week 5: Feelings and worries: how to deal with it in a mindful way
  - Week 6: Mindfulness in everyday life
  - Week 7: Self-Compassion and loving kindness
  - Week 8: Summary and how to develop your own further practice
- Questions from participants
- Formal exercise (breathing anchor, body scan, or yoga)
- Homework (what to focus on the coming week; formal and informal exercises)

In each session, there was a brief introduction to a theme central to mindfulness, participant exchange of experience, formal exercises, and introduction to exercises, such as eating or moving mindfully.

Meeting App (www.acano.com) was used via a technological platform offered by the Norwegian Health Network. This end-to-end encrypted software met the Norwegian government's requirements for secure telecommunications. All participants provided written confidentiality agreements and consented to sit alone under the MBSR-sessions, except for one, who also provided written consent allowing a personal assistant to be present. The assistant provided a confidentiality agreement. The online personnel at SRH had phone numbers to relatives and emergency services. The psychologist leading the intervention could be contacted between sessions if needed and she consulted the study physician (author GM) if necessary. Adverse events, including technical problems, were logged.

Analysis

Descriptive statistics were generated for the sample characteristics and outcome variables. One pain assessment was missed once for one participant during the intervention and was estimated based on the average pain of the two closest assessments (before and after). Although the small sample size limits the power of the statistical analysis, we used the Wilcoxon Signed Rank Test to explore changes between baseline T1, T2, and T3, with $p < 0.05$ being considered statistically significant. The statistical analyses were conducted using SPSS v.22 (IBM Corporation, Armonk, NY, USA).

Qualitative data were analyzed using thematic analysis, to capture important aspects of the data in relation to the research question, and identify levels of patterned response or meaning within the data set (55, 56). The first steps consisted of listening to the audio-recording and getting an overall sense of what was communicated verbally and emotionally. A detailed verbatim transcript was checked against the recording to ensure accuracy, together with the written comments from the evaluation questionnaire of the intervention. The focus group interview consisted of two data sets. In the first data set (experience of outcome of intervention), we generated initial codes for the semantic meaning in the text, secondly reviewed and refined themes in the form of text extracts of each theme, and then defined and named the themes. In the second data set (experience and evaluation of the use of VC) we based the thematic analysis on the themes in Banbury's research (32), highlighting aspects of feasibility and acceptability, such as usability, communication adaption, and accessibility. Since the data from the focus group interviews were a deepening of the written comments in the evaluation questionnaire, these data are reported together.

RESULTS

Participants

Five persons meeting all inclusion criteria and one person without an active pain problem, but with distinct fatigue and emotional distress, consented to participate in the study and were included. One person was excluded due to psychiatric issues. **Table 2** summarizes the demographic characteristics of the six participants. All participants, two men and four women, were Caucasian, and the median age was 34 years (range 20–50). Four persons had independent walking ability in most settings, and two were wheelchair users. All had more than 12 years of education, and all except one were in part-time ($n = 3$) or full-time ($n = 2$) paid jobs. Four persons were single, and two of them were living alone. Two persons were on their usual antispastic- (Lioresal) or analgetic- (paracetamol) peroral medication throughout the study period, tree persons used no medication and one person took up her previous antispastic medication due to increased spasms.

TABLE 2 | Participant characteristics.

Participant	CP diagnosis	GMFCS level	Marital status	Age
1. Theo	Spastic unilateral	I	M, C	30-ies
2. Anna	Spastic bilateral	II	S	30-ies
3. Mimmi	Spastic bilateral	IV	M, C	40-ies
4. Dora	Spastic bilateral	IV	S	40-ies
5. Wilmar	Spastic bilateral	II	S	20-ies
6. Ronja	Spastic unilateral	II	S	20-ies

GMFCS, gross motor function classification system; Marital status, M = married or cohabitant, C = children and S = single.

Symptom Assessments

The median pain intensity at baseline was 3.3 (range: 2.0–4.3). No statistically significant differences were found between pain intensity at baseline and at T2 or T3 (data not shown). The multiple assessments of pain ($n = 16$) demonstrate each participant's trajectory over the study period. As shown in **Figure 2**, pain varied both within and between participants.

Table 3 shows the assessments of pain catastrophizing, stress, emotional distress and quality of life.

During the study period (from T1 to T3) there was a statistically significant decrease in pain catastrophizing, and in negative affect ($p = 0.03$).

Evaluation Questionnaire

All participants except one experienced subjective benefit from the MBSR program, and would recommend it to other persons with CP (see **Table 4**, questions 1 and 5). The participant evaluating no/little benefit elaborated in the focus group that the program did not meet his expectations regarding pain relief, which was the reason why he would not recommend it. All six participants were satisfied with the form and content of the intervention, as well as receiving it via VC. The majority wanted more sessions, and one person wanted a video of the yoga exercises to assist the homework.

Evaluation Questionnaire and the Focus Group Interview -Experience of Outcome (Benefit) of the MBSR

In line with the questionnaire data presented above, all participants evaluated the intervention as useful regarding multiple aspects of everyday coping and stress management. The themes that emerged were all associated with a superordinate theme of *coping benefits*. Moreover, subthemes that emerged were (I) *knowledge of CP and secondary symptoms*, (II) *acceptance of*

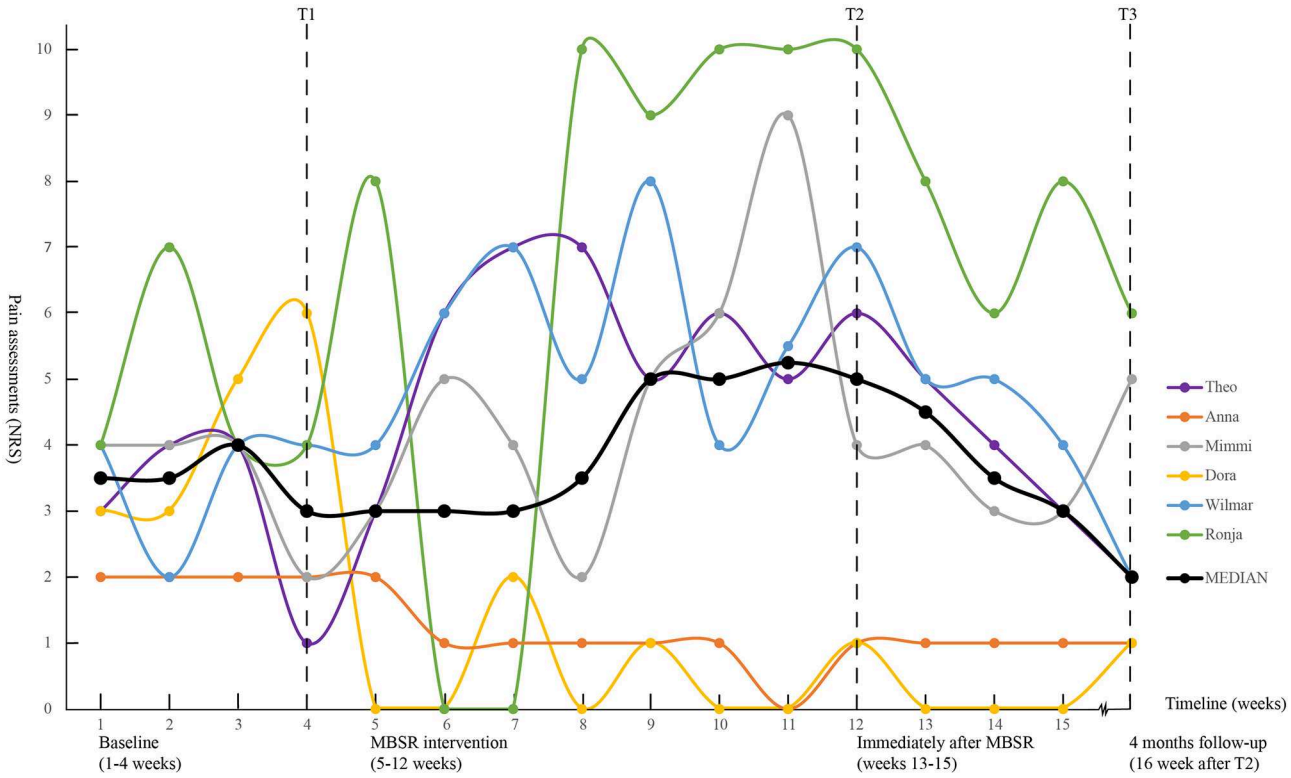

FIGURE 2 | Pain assessment during the study period for all six participants.

bodily limitations and resources, (III) *regulation of emotions*, (IV) *regulation of activity, and rest* and (V) *communication of needs, limits and resources*. These themes had a reciprocal relationship with each other and the superordinate theme.

Knowledge of CP and Secondary Symptoms

The knowledge included learning more about CP and common challenges related to spasms, pain, fatigue, and cognition, from each other and the instructors, particularly for those who had not received CP-oriented health care provision for many years:

> *"People immediately think that I must know everything about CP. I don't! It's the way I was born, the way I've always been. It's my normal situation."* [Anna]

One participant experienced what she first expressed as "bodily shakings" with accompanying pain during the MBSR-intervention. She learnt from the study physician that she was experiencing spasms, and realized that she had ignored these symptoms.

> *"I didn't know what was going on with me. Is it an anxiety attack? Now I know I have spasms because there is something physically wrong with me. I have learned so much, even though it has been a painful process."* [Ronja]

Acceptance of Bodily Limitations and Resources

Increased body awareness and acceptance were commented upon from several as an important benefit, typically expressed as *"better at taking seriously the signals my body sends me"* and *"acceptance of the situation."* This included being aware of sensations in the body, such as pain, which might reflect for example an imbalanced activity level.

> *"It was on account of the pain that I signed up for the course, and it has not helped with that. But I have achieved other things. … What the pain tells me is that there is something wrong with my level of activity. Now I know I ought to work two days instead of three."* [Leo]

One of the two persons who reported increased pain during MBSR said that it was a new experience to consciously attend to bodily signals, which resulted in temporarily increased pain. This participant received three follow ups with one of the interventionists.

> *"It was frightening when the pain increased… But I believe I have been shutting out a whole lot. I may have the pain, but don't focus on it. … So I have to take tiny little steps in teaching myself mindfulness."* [Mimmi]

TABLE 3 | Individual and group results on self-report questionnaires at T1, T2, and T3.

	Time	Theo	Anna	Mimmi	Dora	Wilmar	Ronja	Median value	Inter-quartile Q1, Q3	Range
Pain catastrophizing	T1	13	4	21	12	26	36	17	10.0, 28.5	4–36
	T2	6	5	24	9	22	45	15.5	5.8, 29.3	5–45
	T3	11	3	20	9	17	28	14*	7.5, 22.0	3–28
Stress	T1	26	33	33	36	34	44	33.5	31.0, 38.0	26–44
	T2	28	29	34	27	29	34	29	27.8, 34.0	27–34
	T3	34	25	34	34	33	38	33.8	31.0, 35.0	25–38
Fatigue	T1	14	24	21	11	17	13	15.5	12.5, 21.8	11–24
	T2	11	19	23	5	16	28	17.5	9.5, 24.3	5–28
	T3	11	13	21	5	20	14	13.5	9.5, 20.3	5–21
Anxiety	T1	2	15	9	9	10	11	9.5	7.8, 12.0	2–15
	T2	2	7	10	6	12	14	8.5	5.0, 12.5	2–14
	T3	4	6	9	0	13	13	7.5	3.0, 13.0	0–13
Depression	T1	0	7	4	5	7	4	4.5	3.0, 7.0	0–7
	T2	0	2	4	4	10	1	3	0.8, 5.5	0–10
	T3	1	1	3	4	3	1	2	1.0, 3.3	1–4
Negative affect	T1	12	26	13	11	15	45	14	14.0, 30.8	11–45
	T2	10	14	22	12	16	39	15	11.5, 26.3	10–39
	T3	10	10	10	10	13	41	10*	10.0, 20.0	10–41
Positive affect	T1	32	22	41	46	19	35	33.5	21.3, 42.3	2–46
	T2	33	32	39	50	21	28	32.5	26.3, 41.8	21–50
	T3	33	37	35	50	26	33	34	31.3, 40.3	26–50
Quality of life	T1	6.4	5.8	5.4	5.8	4.7	7.5	6.4	5.2, 6.6	7.5
	T2	6.1	7.4	4.2	6.8	4.9	2.5	6.1	3.7, 7.0	2.5–7.4
	T3	6.4	6.7	5.4	8.2	5.6	6.1	6.4	5.3, 7.0	5.4–8.2

Results are expressed as raw scores. Pain catastrophizing, Pain Catastrophizing Scale (PCS); Stress, The Perceived Stress Scale (PSS-14); Fatigue, The Fatigue Questionnaire (FQ total); Anxiety, Hospitality Anxiety and Depression Scale (HADS-A); Depression, Hospitality Anxiety and Depression Scale (HADS-D); Negative affect, Positive Affect and Negative Affect Schedule (PANAS state negative); Positive affect, Positive Affect and Negative Affect Schedule (PANAS state positive); Quality of life, The Perceived Quality of Life Scale (PQoL).
** Difference T1–T3 sign. at $p < 0.05$.*

Several talked about increased awareness and acceptance that their overall capacity and (psychomotor) speed may be decreased, typically expressed as "*everything goes a little more slowly*." Also, all participants experienced increased awareness of their use of compensatory strategies in everyday life.

> *"Because we have CP, we use different strategies than others to get where we are. I have not been so aware of this before … It feels like we must do more all the time for fear of it not being adequate."* [Wilmar]

Regulation of Emotions

All participants gave examples related to changes in emotional regulation, which included stopping negative self-thoughts, rumination, and staying calmer in stressful situations.

> *"I manage to let trivial things be trivial things and challenges be challenges. I manage to stay calm when things get tough, that is to say, in difficult situations in which I used to lose my temper and vent my anger and frustration."* [Dora]

To stop and focus on breathing was helpful in emotional regulation for several.

> *"I begin crying almost uncontrollably if I feel stressed, am sorry about something, or am extremely happy. … I had an episode where I got angry at a person for a good reason and began to cry. Then I said: 'Just breathe, just breathe!' And I took some breaths until I felt fairly steady. Then I yelled at him: 'Give me a minute to finish crying and calm down, and then I'll deal with it.' I haven't done that before."* [Anna]

Less rumination and a feeling of being relaxed when going to bed were also reported.

> *"In the past, when I went to bed, my head was filled with thoughts, and I lay there brooding. I don't have that problem any longer. Now I have taught myself to turn off the switch."* [Dora]

Regulation of Activity and Rest

All participants reported that the intervention had made them more aware of their need to take breaks when necessary, with a statement such as *"now I take those five minutes,"* which made them feel more relaxed, refreshed or in control.

> *"I sneak in a few extra breaks on the job. If I use the toilet, I stand and look at myself in the mirror and take some deep breaths before I go out again, so that I feel like it has been a real break."* [Anna]

TABLE 4 | Custom-made evaluation questionnaire.

1	What benefit did you have from the MBSR sessions?		Some/great: 2, 3, 4, 5, 6*	No/little: 1
2	Was the theory/purpose of the MBSR clearly explained to you?		No:	Yes: 1, 2, 3, 4, 5, 6
3	Were the exercises clearly explained to you?		Yes: 1, 2, 3, 4, 5	No:
4	Did you get enough practice in formal techniques in the sessions?		Yes: 1, 2, 3, 4, 5, 6	No:
5	Would you recommend MBSR to other people with cerebral palsy?		Yes: 2, 3, 4, 5, 6	No: 1
6	Did you miss more or better defined home tasks?		Yes: 1	No: 1, 2, 3, 4, 5, 6
7	Did you use the MBSR-exercises outside the intervention sessions?		Yes: 1, 2, 3, 4, 5, 6	No:
8	How was the progress in teaching?	Too slow:	Satisfactory: 1, 2, 3, 4, 5, 6	Too fast:
9	How was the amount of MBSR sessions?	Too few: 2, 3, 4, 5	Satisfactory: 1, 6	Too many:
10	How intense were the MBSR sessions?	Too low:	Satisfactory: 1, 2, 3, 4, 5, 6	Too intense:
11	How was it to get the MBSR via web?		Satisfactory: 1, 2, 3, 4, 5, 6	Not satisfactory:
12	Was there something you missed during the MBRS sessions?		Yes:	No: 1, 2, 3, 4, 5, 6

**The numbers represent individual participants that provided this specific response; 1 = Theo, 2 = Anna, 3 = Mimmi, 4 = Dora, 5 = Wilmar, and 6 = Ronja.*

Some told about becoming more conscious to not spend all their energy at once, getting more focused on prioritizing and coping with aspects of attention and peace, as well as cutting back on their need to be perfect.

> *"This course has helped me to be able to focus, to be focused only on the task at hand, complete it, and not think I have to do everything at super speed. … I have also become more conscious of thinking about what I shall prioritize."* [Ronja]

Communication of Needs, Limits, and Resources

The analyses revealed increased awareness and ability to talk about their limits, boundaries, abilities and needs. This was mainly to employers and friends, but also health personnel, because of what was reported as an increased understanding of their health needs due to CP. One individual was requested to perform a task at work and said:

> *"My old self would have said 'yes' and thought that if I didn't say 'yes', I would lose my job. Instead, I replied: 'I'm still a little behind because I've been helping some of my colleagues. Is it all right if I start this new task a week later?' It worked out fine."* [Anna]

Another individual who was in the process of reducing her working hours due to CP-related symptoms had agreed with her boss to speak out more clearly about her true capacity for work.

> *"I have promised him* [the boss] *that we'll have honest communication. I'll not say I'm doing fine if things are not fine. So in a way it has been easier to make accommodations* [on the job] *after this course."* [Ronja]

Feasibility and Experience With Group- and VC-Based MBSR

In the qualitative evaluation of the technical aspects of VC-delivered treatment, the main themes were feasibility and acceptability of technical equipment and solution, exposure and security, communication and social connectedness, and accessibility and adherence.

IT Usability, Training, and Support

There was consensus that the initial technical training at SRH was necessary to overcome worries about technical mastering and barriers.

> *"I don't believe it would have been possible to start this project without having gone through that [the technical aspects] beforehand. … One could feel confident … "* [Ronja]

During the VC sessions two participants reported temporary problems in switching the web-camera on, to adjust the microphone, and some episodes of freezing picture and software problems. Technical problems were not of a magnitude that caused interruption of the sessions. The flexibility of the ICT support team was appreciated by all of the participants.

Privacy and Security

Exposure of privacy in the form of seeing each other's homes was reported as something all participants got used to.

> *"I was a little concerned. Oh, no! The laundry is hanging behind me! Sometimes I had to tidy up beforehand … and after a while, it didn't always seem quite so important."* [Wilmar]

The individual that was troubled by spasms in some VC-sessions felt uneasy about exposing this and agreed with the interventionists to pull a little away from the web-camera when needed. This allowed this person to attend sessions, but also (at least for a period) to hide the need for referral to the physician in the project.

> *"It was, of course, a very good arrangement that if the spasms became too bad, I could move away from the camera. But then I realized that it was perhaps not so fortunate after all. … The disadvantage with VC was that I could protect myself. It took longer to get help."* [Ronja]

No other adverse situations were logged by the interventionists, the ICT team, or the participants. There was a consensus that the IT security in the project was well-taken care of, and participants

were pleased with the amount of information provided on this issue.

Communication Adaption and Social Connectedness

All participants reported that the initial face-to-face meeting laid an important foundation for communicating more freely on VC. Rules for turn-taking were considered necessary, as well as the fact that the interventionists actively invited participants into the communication. There was a consensus that to communicate via VC was satisfactory. The group size was also considered adequate.

> *"I felt that when I was speaking it was like I didn't think there was a screen there. It was a very natural conversation somehow."* [Anna]

All expressed that they had experienced connectedness in the group. Factors contributing to this where described as *"openness among participants," "humor," "trust," "caring,"* and *"exchange of experience with peers."*

The closing of the MBSR VC-sessions was experienced as being too abrupt or sudden, resulting in a feeling if anticlimax, where some felt lonely.

> *"If we had met face to face … it would have ended naturally. We would have cleared the table, made small talk, chatted a little about this and that. Five minutes would have passed and we would have been ready to move on. But online it is just pushing the off-button. Click! And they were gone."* [Anna]

Accessibility and Adherence

The advantages of CV intervention vs. face-to face at a treatment location, were expressed as *"easier logistics," "broke down geographic barriers,"* as well as *"saved mental energy,"* and *"less stressful."* No one reported that they had wanted the intervention face-to-face instead. One participant said adherence on VC was easier on *"bad days."* VC delivery was essential for participation for half of the participants, due to the reasons expressed above, as well as a lack of geographical availability.

> *"Decisive for me was that I never would have had the opportunity to participate without this arrangement. It wasn't possible at my local hospital."* [Mimmi]

Several stressed the importance of having easy access to individual follow-up during the intervention. The interventionists logged two adverse events due to spasticity and increased pain, which led to individual follow-up between sessions. The majority said that an increase from eight to ten or twelve MBSR sessions would have been appropriate, as learning mindfulness was experienced to be a process that took time to process and to implement into everyday life. The length of sessions was considered satisfactory, except for one participant who wanted shorter sessions due to fatigue. Some reported a need to make it clear before the intervention that it might not lead to pain reduction but improved coping (**Table 4**, questions 1 and 5).

DISCUSSION

This pilot study explored the feasibility and results of a group-based MBSR program via VC for adults with CP. The intervention resulted in statistically significant reduced pain catastrophizing and negative affect, while a reduction of pain intensity as such was not obvious. Qualitative data demonstrated benefits in aspects of coping with chronic CP-related symptoms, and that the VC-format provided increased accessibility and social connectedness.

All participants had baseline symptoms of either pain, emotional distress or decreased quality of life, or a combination of these, and half the group had clinically significant fatigue, which is consistent with the known health challenges in adults with CP (10, 57–59). The fact that all participants had a high total stress level highlights that adults with CP experience strain on their coping abilities and adjustments (9, 57).

Catastrophizing thoughts and emotions related to pain are typically understood as the cognitive-emotional experience (39), or reactivity (60) to pain. Reduction of pain catastrophizing has also been found in a Canadian study of a 10 week VC-based MBSR program adapted to chronic pain and delivered to different diagnostic groups (61). The study compared the distant VC MBSR group with a physically present MBSR group and controls. The study indicated that the effect of MBSR on catastrophizing was not hindered by the VC mode of delivery, but that the magnitude of pain reduction might be somewhat lower than when the interventionist is physically present.

In a laboratory setting, Zeidan, and Vago (62) compared experienced and novice meditators with regard to how they rated pain intensity and pain unpleasantness. They found that the intensity of induced pain was rated equally, but that experienced meditators rated the pain as less unpleasant, suggesting that meditation might support non-reactivity to pain. Reduced reactivity to pain might be associated with less catastrophic thinking about pain, which was found in the current study.

An association between pain catastrophizing and negative affect, such as negative attention bias and negative expectation, has been documented (63). One study by Engel et al. (64) found that pain catastrophizing was the coping strategy that most interfered with physical mobility, self-care, recreational, and social activities. Prevention of catastrophizing might thus play a central role in living with chronic pain. This finding in our intervention is in need of replication in larger scale studies.

Some participants experienced increased pain intensity during the intervention. Reasons for this may be multi-faceted. Pain varies naturally, so the results might partly simply reflect natural cycles. However, weekly pain assessments might have contributed to an increased awareness directed toward pain experiences. This might have resulted in an attentional bias, known to have the potential to increase symptoms, especially among pain fearful individuals (65). Also, the intervention itself invites the participants to pay attention to and observe bodily sensations, necessarily giving rise to both comfortable and uncomfortable sensations (66).

The mindfulness literature is sparse about potential symptom increase and unexpected and unwanted effects (UE), such as increased pain and disturbing emotions. However, a multicenter survey of mindfulness and meditation practitioners found that 25% reported UEs; mostly mild and transitory not in need of medical attention. This happened most often in long individual practice in focused attention meditations, and not so frequently in body awareness meditations (67), which dominates MBSR-practice. In a brief MBSR-based program Sass et al. (68) found that high discomfort with emotions, including low tolerance for negative affect, significantly moderated emotional distress reduction. The authors suggest that that the capacity of emotional tolerance should be addressed prior to treatment. This is in accordance with our results, indicating the need to be careful in the selection of VC-based MBSR-candidates. The participants should be informed that the method might not alter pain in itself, and that MBSR may create increased awareness of both comfortable and uncomfortable bodily sensations and feelings before more adaptive coping is developed. However, the qualitative data indicated that even those who experienced more pain felt that the treatment was helpful and that the increased awareness of their functional limitations was for the better in a long-term perspective.

Five interrelated sub-topics of what seemed to be aspects of coping with adult CP appeared from the qualitative data. First, knowledge of CP and secondary symptoms seemed to be a necessary step to decrease insecurity about symptoms, and to enable the use of new coping strategies. Increased knowledge gave participants a platform for acceptance, and communication about their health, resources and needs. This is in line with studies on aging with CP (10, 57), where one review study (10) found that greater knowledge and understanding among individuals with CP improved health-related decision-making. The participants also reported improved skills in communicating their needs and strengths more clearly to employers, friends and health care professionals. In accord with this, Sienko's research (69) on young adults with CP, found that skilled communication of health concerns and needs to medical professionals might enhance locus of control and self-esteem, health, and well-being. According to Mudge et al. (57), to take "charge of help" is central to adults, as the symptoms of CP and secondary conditions will likely change with age, and therefore trigger a need for medical follow-up and adjustments in health care provision.

Also, acceptance of bodily limitations and resources is a significant factor for purposeful coping with CP. One qualitative study (57) showed that acceptance might help the individual to achieve a more realistic picture of what to expect, enabling more positive and adaptive responses to health changes. Brunton and Bartlett (70) describe how bodily awareness, adaptation and regulation among persons with CP is a lifelong process due to changes in symptoms and capacity levels. Increased acceptance seemed to lead to less self-blaming, a connection well-described in positive psychology, where less self-blaming is considered important for better psychological health and more flexible coping (71). Increased acceptance of own strengths and weaknesses and less self-blaming may reflect development of more self-compassion, which was a weekly topic in the adapted MBSR.

When it comes to emotional regulation, the participants described less rumination, being increasingly able to stop negative thoughts and to stay calm in stressful situations. One common factor account for this may be a basic skill in mindfulness training, namely decreased reactivity, where thoughts and feelings are allowed to come and go, without the individual identifying with them or being carried away by them (22, 72, 73). Another strategy for emotional regulation was to establish contact with the "breathing anchor," which was experienced as effective to stop rumination. This strategy is understood as a form of attentional control, a well-documented aspect of mindfulness that might contribute to downregulation of uncomfortable emotions (74).

The theme "regulation of activity level and rest" also included being aware that bodily symptoms might signal a need to adjust. Improved coping with the need to balance rest and activity, might in turn help reduce strain that is contributing to pain (14). This is an adaptation process that might take more time than the current intervention allowed for. A study of walking children and adolescents with CP and controls, concluded that the strain from walking, close to or above anaerobe threshold for many, might explain fatigue (75). This type of strain is probably present for adults as well. Five of the participants in our study were walking or partly walking, and two of these had fatigue above clinical levels. To take short breaks and include the "breathing anchor" seemed to be helpful to feel bodily and mentally refreshed.

Regulation of attention, in doing one thing at the time, and staying task-focused, was experienced as one of the most important gains from the MBSR-intervention for one participant. This is not surprising, as research on mindfulness and yoga proposes a modification of attentional subsystems in experimental tasks assessing attention in both healthy adults (76) and children with CP (77). This effect might be particularly important in patient groups were attentional capacity is impaired due to brain injury.

Feasibility and Acceptability of Group- and VC-Based MBSR

Technical training before MBSR intervention and access to support during the intervention was considered necessary. This is in accordance with Banbury et al. (32) who found that this is central to the acceptability of home-based VC in groups. It might also be of particular relevance to participants who, due to CP, have sensory, motor, cognitive, or other challenges that result in a need for individual adaptations. The participants had little concern about privacy issues, such as showing a part of their home along with themselves on the camera, which is also in line with Banbury et al. (32). Surprisingly, the literature is sparse concerning aspects of security in videoconferencing groups, but a Danish article about challenges in future telehealth provision (78) considers this to be a central theme. This pilot study indicates that IT security and the participants' respect for confidentiality are central to establishing a sense of trust, where the group members feel they can communicate freely.

Communication adaptation was evaluated as satisfactory, and only one participant experienced that communicating via VC was cognitively demanding. This is also in line with Banbury et al. (32), who found that only a few felt uncomfortable using VC to communicate with others. Clear guidelines for not interrupting each other and to speak slowly seems to be necessary, and is often a part of VC group protocols. This might be of importance if participants have some motor speech problems, such as in this group, where one participant had slow speech and dysarthria.

The fact that VC did not seem to hinder the establishment of group connectedness is in line with one of the main findings from Banbury et al. (32, 79). High attendance rate, as in our study, might enhance cohesiveness, and also indicates high feasibility. The literature is not conclusive regarding the need to meet face-to-face before VC (32). However, it may take some time before some participants feel at ease with online meetings, and in this study, participants reported that meeting face-to-face was helpful. Also, the interventionists got to know the participants, which made individual adjustments and follow-up between sessions easier. This is in line with Greenhalgh et al. (33), who found that video consultations appear to work better when the clinician and participant already know and trust each other. The VC mode of delivery was appreciated by the participants due to the reduced energy expenditure, time spent on traveling, and because it was easier to combine treatment with work and daily life. This all rendered the intervention accessible to persons who did not have access to this kind of treatment in their communities. These findings are also in line with Banbury et al., who argue that using VC might overcome known mobility, time, and distance related barriers (32). The participant feedback interestingly indicated a need to pay particular attention to how sessions are closed. Closing of VC sessions is absolute, with no help from closing rituals that often accompany face-to-face conversations. Also, some participants might have activated uncomfortable thoughts, feelings and bodily sensations, and need help from an interventionist to downregulate before session closure. The VC format itself might also be a barrier to noticing this type of reactions. To our knowledge, these themes have not been addressed in the literature on group-based VC interventions before.

Limitations and Strengths

The major limitation of this study is the small sample size and lack of a control group. This hampers the generalizability of findings, and statistical analysis should be interpreted as crude indications of possible areas of interest in future studies. On the other hand, as the literature on the use of VC in the CP-population is limited, it was considered necessary to explore feasibility and efficacy in a pilot study before establishing a large scale randomized controlled study. The group had a high educational level, probably not representative for the overall CP population. The interventionists conducted the focus group interview, which might have affected what the participants chose to share in their evaluations. One strength of the pilot study was that the MBSR-program was led by a psychologist and physiotherapist with longstanding experience with the CP population. This included familiarity with potential challenges such as cognition, emotional issues, and restrictions in movements, which made it easier to individually adapt the VC sessions. In addition, the ICT team consisted of health personnel, and the participants had individual adaptations and training in technical equipment before the intervention. Also, the participants had access to individual follow-up during the intervention, and there were no drop-outs. In addition to qualitative methods, the pilot study used standardized questionnaires for outcome assessment. We are not aware of any other studies exploring MBSR delivered in a group and by VC in adults with CP. Even if the study is exploratory, we consider the results relevant in informing future study protocols.

CONCLUSION

This pilot study found that an adapted 8 week MBSR program via VC was beneficial in managing pain catastrophizing and negative affect among adults with CP. The qualitative data indicate that the intervention and VC delivery was feasible with no major adverse effects. Group-based MBSR delivered via VC seems appropriate to reduce energy cost and increase accessibility, and has potential as a supplementary health service program for adults with CP. This pilot study provides important information in the planning of future studies with a more rigorous scientific design on group-based VC intervention programs for adults with CP and other patient groups with long-term disability.

Recommendations for a Further MBSR Program via VC

Because CP is a complex condition often associated with pain, fatigue, and stress, it seems useful to integrate psychoeducation about these in an adapted MBSR. An increase from eight to ten sessions may, therefore, be fruitful. The closing of each MBSR session on VC needs sufficient time and careful monitoring. It is also important to identify those who may be at risk of experiencing negative treatment effects. This could be achieved through an individual assessment before the intervention, as well as by offering individual follow-up during the intervention. Because qualitative data indicated increased self-acceptance and less self-blaming, which may reflect self-compassion, future studies should include an outcome measure regarding self-compassion.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author, (HH: helene.hoye@sunnaas.no), upon reasonable request.

ETHICS STATEMENT

This study involving human participants were reviewed and approved by the Regional Committee for Medical Research Ethics, South-Eastern Norway (216/962). The

patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

HH, RJ, JH, HS, ST, and GM have been part of the research group from the start, and have all contributed to the planning, data collection, and data analysis. First author HH led the intervention, JH was co-therapist in the intervention, while HS was responsible for the technical solutions and support provided. ML has taken actively part in data analysis and writing of the paper. While first author HH has been mainly responsible for writing the manuscript, all authors have contributed significantly in the writing process, and have read the final version of this manuscript.

FUNDING

The project was partly funded from South-Eastern Norway Regional Health Authority's project Digital services for inhabitants and Innovation projects (17/00264-15).

ACKNOWLEDGMENTS

We thank all participating adults with CP.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

SYSTEMATIC REVIEW
published: 06 May 2020
doi: 10.3389/fneur.2020.00354

The Role of Engagement in Teleneurorehabilitation: A Systematic Review

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The growing understanding of the importance of involving patients with neurological diseases in their healthcare routine either for at-home management of their chronic conditions or after the hospitalization period has opened the research for new rehabilitation strategies to enhance patient engagement in neurorehabilitation. In addition, the use of new digital technologies in the neurorehabilitation field enables the implementation of telerehabilitation systems such as virtual reality interventions, video games, web-based interventions, mobile applications, web-based or telephonic telecoach programs, in order to facilitate the relationship between clinicians and patients, and to motivate and activate patients to continue with the rehabilitation process at home. Here we present a systematic review that aims at reviewing the effectiveness of different engagement strategies and the different engagement assessments while using telerehabilitation systems in patients with neurological disorders. We used PICO's format to define the question of the review, and the systematic review protocol was designed following the Preferred Reported Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. Bibliographical data was collected by using the following bibliographic databases: PubMed, EMBASE, Scopus, and Web of Science. Eighteen studies were included in this systematic review for full-text analyses. Overall, the reviewed studies using engagement strategies through telerehabilitation systems in patients with neurological disorders were mainly focused on patient self-management and self-awareness, patient motivation, and patient adherence subcomponents of engagement, that are involved in by the behavioral, cognitive, and emotional dimensions of engagement. Conclusion: The studies commented throughout this systematic review pave the way for the design of new telerehabilitation protocols, not only focusing on measuring quantitative or qualitative measures but measuring both of them through a mixed model intervention design (1). The future clinical studies with a mixed model design will provide more abundant data regarding the role of engagement in telerehabilitation, leading to a possibly greater understanding of its underlying components.

Keywords: engagement, self-management, patient activation, digital technologies, teleneurorehabilitation

OPEN ACCESS

Edited by:
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Sant'Anna Institute, Italy

Reviewed by:
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Hannes Devos,
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Specialty section:
This article was submitted to Neurorehabilitation, a section of the journal Frontiers in Neurology

Received: *03 December 2019*
Accepted: *09 April 2020*
Published: *06 May 2020*

Citation:
Matamala-Gomez M, Maisto M, Montana JI, Mavrodiev PA, Baglio F, Rossetto F, Mantovani F, Riva G and Realdon O (2020) The Role of Engagement in Teleneurorehabilitation: A Systematic Review. Front. Neurol. 11:354. doi: 10.3389/fneur.2020.00354

INTRODUCTION

In the field of neurorehabilitation, one of the main objectives after a brain or nerve injury is to develop rehabilitation strategies directed at the recovery of functional skills by enhancing neuroplasticity (2). Even though the type of intervention, intensity, and number of sessions are known to be important in task-specific rehabilitation trainings (3), it is known that the role of engagement is key for enhancing neuroplasticity, and to facilitate functional recovery in patients with neurological disorders (2, 4). In this regard, some studies observed that by increasing patients' attention and interest toward rehabilitation training, there is an updating and modification at a neurological level, which leads to improving functional outcomes (5). However, to achieve such positive functional outcomes in neurorehabilitation, the nervous system has to be engaged and challenged (5, 6). From a neurobiological point of view, several studies have shown how engagement may increase neural activity in different cortical areas such as (2) the orbitofrontal regions, that integrate information from sensory and motivational pathways to generate pleasure, (3) the ventral striatal dopaminergic systems, and (4) the anterior cingulate cortex, which holds attention during demanding task execution (7). Even though there are not enough studies using neuroimaging techniques to demonstrate the effects of engagement in neuroplasticity for rehabilitation, a large amount of studies using mental practice techniques, enriched environments, and attentional and motivational strategies in which patients become active actors of the rehabilitation training, corroborates the relationship between engagement and neuroplasticity (8–10). Concerning this, the growing development of technology in the last decade lead to the introduction of new digital systems in rehabilitation through which it is possible to provide different sensory stimuli enhancing patients' resources such as attention and motivation. Thus, digital technologies in rehabilitation are directed to providing information and/or support emotional, behavioral, or physiological features of the pathology within an enriched and stimulating environment (11–14). One interesting feature of digital technologies in rehabilitation is the opportunity to apply technology-based interventions to provide a rehabilitation service through digital and telecommunication technologies during the hospitalization period, or at home after discharge from the hospital (15). Such application of digital technologies for rehabilitation is commonly known as telerehabilitation (16). Moreover, through telerehabilitation systems is possible to engage patients by providing them an online (or offline) feedback of their outcomes through a double communication loop (17, 18). This type of communication combines remote monitoring of patients' performance with clinicians' appropriate responses by adapting and personalizing the planned rehabilitation activities, and empowering patients toward the targeted rehabilitation aim (18, 19). Further, through these types of telerehabilitation systems, clinicians can supply the needs of the patients in long-lasting rehabilitation programs after the hospitalization period, allowing them to remain involved in social and productive life even though of their clinical condition (17). Moreover, through telerehabilitation systems clinicians have the possibility of delivering long rehabilitation trainings in an enriched digital environment at patients' homes while saving a big amount of sanitary costs (20). Thus, the use of telerehabilitation systems can enhance the patients' engagement by conducting their rehabilitation training at home. However, how to enhance engagement and what engagement is when using telerehabilitation systems in patients with neurological disorders is not clear enough. Due to this, the following section aims to clarify some components and subcomponents of engagement at a clinical level.

Patient-Centered Medicine and Engagement

When we refer to patient engagement in the clinical field, we have to refer to patient-centered medicine (PCM). These two concepts are associated given that PCM considers a patients active participation in the clinical process as pivotal, instead of only considering the clinical professionals' point of view (21). In that context, patient engagement was considered as a concept to qualify the exchange between patients' demands and clinicians' supplies (22). Further, in healthcare, the term "engagement" came to indicate a renewed partnership between patients and healthcare providers (23). Then, the main goal of engaging patients in their clinical process can be identified in making them conscious of the management of their health status and illness, and to provide more positive outcomes in healthcare (24). Indeed, during the clinical process, patient engagement is a key factor in making them feel like participants in the therapeutic process that will lead to better adherence to the therapy, patient sensitization, and patient knowledge and empowerment (25). Even though the term "engagement" seems clear enough by itself, it involves different factors that have to take into consideration when engaging patients in a therapeutic process. Specifically, the involved factors in engagement are the following: participation and decision making, compliance and adherence, self-management, patient empowerment, and patient activation.

Participation and Decision Making

One of the main objectives for the improvement of the quality of health services defined by Entwistle and Watt (26) is the ability to involve patients in their therapeutic process by collaborating with the healthcare professionals. Two main factors have been defined for involving patients in clinical practices: patient participation and patient decision making. The first, patient participation, is considered a psychological component that focuses on identifying emotional and cognitive factors to enhance the active participation of the patients in clinical decision making (27). The second one is centered on the clinical and relational skills of the healthcare professionals in involving patients in clinical decisions (28, 29). Altogether, when referring to engagement in a clinical context, one intends to increase the communication between clinicians and patients to motivate patient participation throughout the clinical process. That means, giving the patients enough information about their illness to become more independents in their healthcare routine. Then, an

engaged patient is a patient that can participate in the clinical decision making and healthcare routine, but also a patient able to actively participate in the global healthcare system promoting new forms of assistance, for example by using new technology systems (30).

Compliance and Adherence

Other factors embedded in patient engagement are "compliance" and "adherence" that refer to the adaptive behaviors of patients in following medical prescriptions or in following the healthcare routine (31). Although these two factors are often presented together, there are some differences between them. While "compliance" is related to patients' ability in adapting their life routine with a more passive/dependent attitude to the clinicians' indications (32), "adherence" is related with patients participation as an active actor in the communication exchange with the clinicians in which patients' and clinicians' plan together the patients care routine (33). Hence, the level of compliance and adherence to the clinical process depend on patients' attitudes and behaviors in accepting or disagreeing with the clinicians' prescriptions, moving the concept of patients' engagement toward a balance between patients' demands and clinicians' supplies (30).

Self-Management, Patient Empowerment, and Activation

Self-management is referred to as the patients' ability to manage symptoms, treatments, psychological, and psychosocial consequences of their pathological condition, as well as the ability to manage the cognitive, behavioral, and emotional responses, derived from their clinical condition, to reach a satisfactory quality of life (34, 35). Indeed, self-management is considered a positive outcome of patient engagement during the clinical process. Moreover, patient empowerment is also considered an important positive outcome during the patient engagement process. It is known that the term "empowerment" refers to psychological resources through which patients can control their clinical condition and the related treatments (36, 37). Thus, by providing the patients an educational healthcare process, they can recover agency and beliefs of self-efficacy over their health condition increasing their autonomy at the same time (38). Even though the concept of "empowerment" and the concept of "engagement" are strongly related, "empowerment" is considered an outcome of a mainly cognitive boosting process of patients, related to their knowledge of the clinical condition, while "engagement" also sustains the emotional aspects regarding to the acceptance of the patients clinical conditions and the behavioral skills to manage it (30). Finally, patient activation is related to the capacity of the patients in managing their clinical condition and the ability to interact with the healthcare system based on their level of knowledge (39, 40). It is suggested that an increase in patient activation leads to an increase in healthy behaviors and adherence to the clinical process (23). Patient activation has been defined by Hibbard et al. (23) as composed of four phases: (1) the passive activation level, where patients are not aware of their role in their health management; (2) where patients starts to create their resources and knowledge about their health condition; (3) where patients can elaborate *ad hoc* responses to the problems related to their clinical condition; and (4) where patients can maintain their new lifestyle behaviors for long-term periods, even when they are under stressful situations. Then, following the later commented phases, Hibbard et al. created the patient activation measure (PAM) to assess patient activation (23).

Hence, patient engagement considers not only the clinical environment but also the non-clinical contexts such as patients' daily routines, activity routines, and the acceptance of their clinical condition outside the hospital, by exploring the dialogue between the supplies and demands of the healthcare services (41). Concerning this, the use of new digital technologies to achieve the patients' engagement during and after the hospitalization period has been proposed (42).

Technology for Patient's Engagement in Neurorehabilitation

Today the development of new technologies has paved the way for their use for clinical purposes, especially to enhance patients' engagement in their healthcare routine (43). Recently, it has been demonstrated that the use of new digital technologies can modulate the dimensions described by Seligman (44) for positive psychology. Digital technologies have been considered essential for illness prevention such as courage, future-mindedness, optimism, interpersonal skill, faith, work ethic, hope, perseverance, flow, and joy (42). In this regard, it is known that the use of virtual environments and serious games can induce positive emotional states, creating new virtual environments for human psychological growth and well-being (45). Following the model proposed by Frome (46), four factors have to be present to induce positive emotions by using such virtual or serious games: a narrative factor, by using roleplaying through which is possible to feel the emotions of the virtual character; game-playing factor, by providing the feeling of frustration or satisfaction when winning or losing the game; the simulation factor, meaning that the game has to provide engaging activities; and the aesthetics factor, referring to the artistic features of the game. These factors can promote engagement of the users by using different technological sources such as mobile e-health (47), and e-learning platforms (48), biofeedback systems (49), virtual reality systems (50, 51), and playing videogames (45), at their own home.

In addition, new rehabilitation protocols, including the use of new technologies, have been developed in the neurorehabilitation field (52, 53). Particularly, the use of new technologies in neurorehabilitation, such as telerehabilitation systems, allows the patients to continue with their healthcare process at home (19, 54). In the field of neurorehabilitation, the rehabilitation and healthcare routine after the hospitalization period is complex, requiring a multidisciplinary coordination (55, 56). Telerehabilitation systems in neurorehabilitation allow a large number of people with neurological disorders—who often have limitations due to limited mobility and to costs associated with travel—to continue with their healthcare process at their own home, minimizing the barriers of distance, time

and costs, and receiving continued support by the clinicians remotely (57, 58). The feasibility and efficacy of telerehabilitation systems in neurorehabilitation have been documented in patients with different neurological conditions such as patients in a post-stroke phase (59–61), Parkinson Disease (18, 62, 63), and Multiple Sclerosis (18, 64). Nevertheless, the role of engagement and the different factors to engage patients with neurological disorders in the telerehabilitation training during the rehabilitation period have not yet been deeply investigated. Hence, this systematic review aims at reviewing the effectiveness of different engagement strategies and the different engagement assessments while using telerehabilitation systems in patients with neurological disorders.

METHODS

A systematic review of the scientific literature have been conducted in order to identify different engagement strategies, as well as studies reporting engagement assessment methods when using telerehabilitation systems in patients with neurological disorders. The systematic review protocol was designed following the Preferred Reported Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (65).

Data Sources and Search Strategy

According to the PICO format to formulate the foreground question of this systematic review (66), the review question has been defined as, "in adults with neurological disorders, is the role of engagement for telerehabilitation interventions, compared to treatment as usual, effective in improving neurorehabilitation intervention." Bibliographical data was collected on July 4, 2019, by using the following bibliographic databases: PubMed, EMBASE, Scopus, and Web of Science. For each database, we used the following combination of research keywords: (1) ("engagement" OR "motivation" OR "activation" AND "telerehabilitation"); (2) ("engagement" OR "motivation" OR "activation" AND "telehealth"); (3) ("engagement" OR "motivation" OR "activation" AND "telemedicine"); (4) ("engagement" OR "motivation" OR "activation" AND "telecare"). See the detailed search strategy in **Table 1**. Only full-text available articles were included in our research (conference paper were excluded), studies citation were retrieved independently for each string of keywords across all databases. Finally, the first list of the collected studies during the bibliographic research was exported to Mendeley to remove duplicated studies. Then the list of studies without duplicates was imported to Rayyan (67) for the title and abstract screening, following the specified inclusion or exclusion criteria for study selection (see section Study Selection and Data Collection) by one reviewer (M.M.G). The final list of the selected studies was sent to leading experts in the field for suggestion and identification of any missing studies, and no studies were added.

Study Eligibility Criteria

The present review aims at reviewing the effectiveness of different engagement strategies and the different engagement assessments while using telerehabilitation systems in patients with neurological disorders. Then, the selected studies had to investigate engagement while using telerehabilitation systems in adult patients with neurological disorders. Bibliographical research was limited to studies using humans and written in English. Further, the selected studies had to accomplish the following inclusion criteria:

(1) Telerehabilitation interventions must have been directed to engage patients in their healthcare routine. Interventions directed to engage other stakeholders such as medical staff, hospital managers, and others were excluded.

(2) Telerehabilitation interventions must have been directed to a group of patients, with a between or within-group study design. Single case studies have been excluded.

(3) Telerehabilitation interventions have been directed to assess one or more components of patient engagement.

Study Selection and Data Collection

One reviewer (M.M.G.) conducted the final selection of the studies for full text analyses. The following keywords were considered as inclusion criteria for selected articles in Rayyan (67): neurorehabilitation, neurological patients, patients, participation, adherence, self-management, empowerment, activation, telerehabilitation, telehealth, telemedicine, telecare, e-health. Further the following keywords were considered as exclusion criteria: no engagement, no neurological patients, animal studies, and review studies. Then, the final selected articles that accomplished the inclusion criteria were analyzed by three reviewers (M.M.G., M.M., and J.M.) for independently full-text analyses. The final selected studies were discussed among the three reviewers in order to solve minor discrepancies about the study selection criteria that had been solved by consensus.

Risk of Bias Assessment

To the risk of bias assessment, the reviewers followed the guideline of the Cochrane Collaboration risk of bias tool according to the latest version of the risk of bias tool (RoB2) statement (68). All three reviewers (M.M.G, M.M, and J.M) independently evaluated the studies for risk of bias, and disagreements were resolved through consensus (**Table 2**).

Data Extraction

Each selected study was coded according to the following thematic categories: (1) Authors and Year of publication; (2) Clinical condition (N); (3) Patients characteristics; (4) Sample size; (5) Control group; (6) Type of engagement; (7) Engagement assessment; (8) Main results (**Table 3**). All three reviewers followed the coding studies criteria to analyze the final selected studies. Further, the TiDER checklist has been used for reporting detailed information about research interventions (87). Specifically, the following points of the TiDER checklist have been reported: (1) why (aim of the study), (2) what (materials), (3) who provided, (4) tailoring, and (5) intervention adherence (**Table 4**).

TABLE 1 | Data search strategy.

"Engagement" OR "motivation" OR "activation" AND	PubMed	EMBASE	Scopus	Web of science	
	Abs/Tit	Article	Article	Article	Total_keyword
Telerehabiliation	41	52	275	59	427
Telehealth	216	1115	967	271	2569
Telemedicine	293	821	2461	391	3966
Telecare	32	67	854	38	991
Total	582	2055	4557	759	7953
Total to analyze without duplicates					4618

RESULTS

Study Selection

Seven thousand nine hundred and fifty three studies were found, including the above commented key words in section Data Sources and Search Strategy, and including the above-specified inclusion criteria words (section Study Selection and Data Collection). After removing duplicate studies, a total of 4,618 studies were included for the title and abstract screening into the Rayyan software. Of 4,618 non-duplicate studies, 4,464 studies did not accomplish the described study eligibility criteria. Subsequently, 82 studies were selected for full-text analyses. Of the 82 full text analyzed studies, only 18 studies were identified as suitable with the above-described inclusion criteria. See **Figure 1** for a flow diagram depicting the study selection process.

Of 82 studies, only 18 studies included engagement strategies and engagement assessment either as a primary or secondary outcome after the telerehabilitation training in patients with neurological disorders.

Study Characteristics

The final eighteen selected studies were described in detail. Further, **Table 3** shows the characteristics of each of the selected studies. Ten studies compared patients with neurological disorders with healthy subjects or with other group of patients (69, 72, 74, 76–79, 82, 85, 86). Among the selected studies four studies were conducted in patients with Parkinson Disease (PD) (72, 78, 83, 86), four in patients with stroke (69, 71, 73, 74), and five studies were conducted in patients with multiple sclerosis (MS) (75, 77, 81, 82, 84). All the selected studies used engagement strategies in their telerehabilitation program, as well as engagement assessment measures. Particularly, eight studies used interviews to obtain qualitative data of patient engagement (69, 71, 74, 75, 82–85), six studies used functional assessment scales (70, 72, 73, 76, 80, 81), and three studies used paper or digital diary reports (77, 78, 86).

Moreover, following the TiDER checklist for reporting research interventions (87), the following points have been reported in **Table 4**: (1) why (aim of the study), (2) what (materials), (3) who provided, (5) tailoring, and (6) intervention adherence. (2) Out of the eighteen analyzed studies, thirteen studies aimed at investigating the effectiveness, usability, feasibility, reliability, and acceptability of the telerehabilitation system (70–75, 77–79, 82–84, 86), one study aimed at investigating the sense of co-presence between the therapist and patients through the telerehabilitation system (69), three studies aimed at investigating changes in self-management, self-determination, and self-motivation after the telerehabilitation period (76, 81, 86), and finally one study aimed at assessing possible changes in aphasia severity after the telerehabilitation period (80). (3) Five studies used a computer-based telerehabilitation system (69, 73–75); three studies used a tablet set-up as a telerehabilitation platform (70, 71, 78); three studies used patients smart phones applications for psychological or motor telerehabilitation programs (72, 81, 86); three studies used phones as a set-up for telephone-based telerehabilitation intervention (76, 79, 82); finally, three studies used an online web-platform as an internet-based telerehabilitation intervention (77, 80, 85). (4) Out of the 18 selected studies, nine studies involved therapists (physiotherapist, psychologist, medical, coach therapist) or medical doctors in the administration of the telerehabilitation program (69, 74–76, 79, 80, 82, 84, 85); four studies involved trained researchers in the administration of the telerehabilitation program (72, 73, 78, 83), two studies described a patients self-administered telerehabilitation program (70, 71), and three studies did not specify who was involved into the telerehabilitation program (77, 81, 86). (5) Out of the 18 analyzed studies, only three studies adjusted the difficulty levels of the telerehabilitation program automatically according to the progress of the patients among the rehabilitation period (69, 73, 74). (6) Out of the 18 analyzed studies, only one study did not assess adherence to the intervention (70). Among the other 17 studies, 11 studies used semi-structured or unstructured interviews to assess patients adherence to the telerehabilitation program (71, 72, 75, 76, 78–84). Four studies used questionnaires (74, 75, 77, 86), two studies used the assessment report collected from the mobile or tablet rehabilitation application (78, 86), and one study used the online counseling feedback to assess patients adherence to the telerehabilitation program (85). In addition to the latter commented points, **Table 4** shows more detailed information about the research intervention of each study.

TABLE 2 | Risk of bias assessment.

References	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias): self-reported outcomes	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Yeh et al. (69)	High	High	High	Low	Low	Low	High: small smaple size/no control group/no homogeneous clinical sample
Llorèns et al. (70)	High	High	High	Low	Low	Low	High: small sample size/no control group
White et al. (71)	High	High	High	High	Low	Low	High: small sample size/no control group/only interview assessment
Ferreira et al. (72)	High	High	High	Low	Low	Low	High: small sample size
Nijenhuis et al. (73)	High	High	High	Low	Low	Low	High: small sample size/no control group
Lloréns et al. (74)	Low	Low	Low	Low	Low	Low	Low
Palacios-Ceña et al. (75)	High	High	High	High	Low	Low	High: small sample size/no control group/only interview assessment
Houlihan et al. (76)	Low	Low	Low	Low	Low	Low	Low
Engelhard et al. (77)	High	High	High	Low	Low	Low	High: no control group
Lai et al. (78)	High	High	High	Low	Low	Low	Low
Skolasky et al. (79)	Low	Low	Low	Low	Low	Low	Low
Pitt et al. (80)	High	High	High	Low	High	Low	High: small sample size/no control group
D'hooghe et al. (81)	High	High	High	Low	Low	Low	High: no control group
Dennett et al. (82)	Low	Low	Low	Low	Low	Low	Low
De Vries et al. (83)	High	High	High	High	Low	Low	High: small sample size/no control group/only interview assessment
Thomas et al. (84)	High	High	High	High	Low	Low	High: small sample size/no control group/only interview assessment/no homogeneous clinical sample
Chemtob et al. (85)	High	High	High	High	Low	Low	High: small sample size/only interview assessment
Ellis et al. (86)	Low	Low	Low	Low	Low	Low	Low

High, High risk of bias; Low, Low risk of bias.

Risk of Bias

All studies except five presented a high risk of bias in some of the assessed factors in this systematic review (74, 76, 79, 82, 86). **Table 2** shows the results of the risk of bias assessment of this systematic review. All the studies included in this systematic review reported the sampling method. However, only five out of 18 studies presented a randomized control trial study design, including a control group for treatment comparisons (74, 76, 79, 82, 86). Ten studies presented an small sample size to represent the results obtained after the treatment period (69–73, 75, 80, 83–85). Five studies based their results on the analyses of interviews conducted to the patients without analyzing any other clinical

TABLE 3 | Overall studies characteristics.

References	Clinical condition [total sample size]	Patients characteristiscs	Case vs. control group [size]	Control group [type]	Case group [type of engagement]	Engagement assessment	Main results
Yeh et al. (69)	Stroke, TBI, SCI [*N* = 14]	Unspecified	[14 vs. –]	No	Emotional engagement (secondary outcome of the study)	The mood was measured with the POMS questionnaire; experience of "presence" in the telerehabilitation environment, willingness to persist with therapy, and a telerehabilitation usability questionnaire	Patients felt less efficacious in continuing therapy after participating in the telerehabilitation game compared to their reported perseverance self-efficacy before the game and showed a decreased willingness to persist in therapy regardless of fatigue after the gameplay.Telerehabilitation significantly enhanced stroke patients' psychological states
Lloréns et al. (70)	ABI [*N* = 10]	Chronic phase (> 6 months)	[10 vs. –]	No	Self-awareness game, that consist in answering questions related to knowdledge (anatomical and pathological matters), reasoning (situational exercises), action (role-playing), or cohesion (jokes and sayings), in a competitive context	Self-Awareness Deficits Interview (SADI) Social Skills Scale (SSS)	The VR game improved self-awareness and the social cognition deficits in patients with ABI after the 8 months training period
White et al. (71)	Stroke [*N* = 12]	Unspecified	[12 vs. –]	No	Face-to-face sessions aimed to provide orientation to the iPad, educate toward therapist recommended rehabilitation Apps and access to other tablet technology features	Telephonic semi-structured interviews	Stroke survivors experienced increased participation in therapeutic activities, increased socialization, and less inactivity and boredom
Ferreira et al. (72)	PD [*N* = 33]	Mild-to-moderate stage (Hoehn and Yahr score 1–2.5)	[22 vs. 11]	Usual care	Biofeedback from the system and weekly telephonic interviews	Semi-structured interviews to assess willingness to continue in the study, satisfaction with the SENSE-PARK System, changes in health status or medical condition, adverse events, feedback messages, and doubts about the system	Motivation to wear such a system can be increased by providing direct feedback about the individual health condition
Nijenhuis et al. (73)	Stroke [*N* = 24]	Chronic phase (> 6 months)	[24 vs. –]	No	Video-game and remote supervision of the clinicians	Intrinsic Motivation Inventory (IMI)	Participants were able and motivated to use the training system independently at home. Usability shows potential, although several usability issues need further attention
Lloréns et al. (74)	Stroke [*N* = 45]	Chronic phase (> 6 months)	[30 vs. 15]	Training at the hospital.	Engagement as a secondary outcome	Usability Scale (SUS) Intrinsic Motivation Inventory (IMI)	Both groups considered the VR system similarly usable and motivating

(Continued)

TABLE 3 | Continued

References	Clinical condition [total sample size]	Patients characteristiscs	Case vs. control group [size]	Control group [type]	Case group [type of engagement]	Engagement assessment	Main results
Palacios-Ceña et al. (75)	MS [*N* = 24]	Unspecified	[24 vs. –]	No	Video-game and tracked movement feedback	Unstructured interviews	Four main themes emerged from the data: 1) regaining previous capacity and abilities. 2) Sharing the disease, 3) adapting to the new treatment. This refers to the appearance of factors that motivate the patient during KVHEP
Houlihan et al. (76)	SCI [*N* = 126]	Traumatic SCI, chronic phase (≥1year postinjury)	[84 vs. 42]	Usual care	Peer health coach (PHC), who acts as a supporter, role model, and advisor	Patient Activation Measure (PAM)	Intervention participants reported a significantly greater change in PAM scores compared with controls. Participants reported a significantly greater decrease in social/role activity limitations, greater services/resources awareness, greater overall service use, and a greater number of services used
Engelhard et al. (77)	MS [*N* = 31]	MS with Expanded Disability Status Scale ≤ 6.5	[31 vs. –]	No	A dedicated "Symptom Tracker" page allowed subjects to compare severity between symptoms and view recent trends	Completion of the web-exercises	52% of the subjects reported improved understanding of their disease, and approximately 16% wanted individualized wbPRO content. Over half of perceived well-being variance was explained by MS symptoms, notably depression, fatigue, and pain
Lai et al. (78)	PD [*N* = 30]	Mild-to-moderate stage (Hoehn and Yahr score 1–3)	[20 vs. 10]	Self-regulated exercises	To instruct participants on proper exercise techniques to increase mastery, discuss barriers or issues with the participants' ability to attend the exercise sessions, help participants set achievable goals to complete the exercise prescription, provide verbal encouragement to achieve the desired exercise workload	Measures of adherence included four variables: number of sessions performed, time of exercise, and attendance	Internet supervised training at home could promote stronger program adherence than self-managed home-exercise training. The telehealth system, telecoaches provided a sense of companionship and accountability and bolstered participants' confidence to overcome several impediments to participation
Skolasky et al. (79)	LSS [*N* = 182]	post-surgery phase	[122 vs. 60]	Usual care	Telephone-based intervention engagement	Engagement is a secondary outcome	Health behavior change counseling improved health outcomes after the surgical procedure through changes in rehabilitation engagement

(Continued)

TABLE 3 | Continued

References	Clinical condition [total sample size]	Patients characteristiscs	Case vs. control group [size]	Control group [type]	Case group [type of engagement]	Engagement assessment	Main results
Pitt et al. (80)	Aphasia [*N* = 19]	Unspecified	[19 vs. –]	No	Video-conferences to create opportunities for communicative success, to share personal life history, and to provide support for living successfully with aphasia through networking with others	Quality of Communication Life Scale. Communicative Activities Checklist Engagement a secondary outcome	Improvements in communication-related quality of life increased engagement in communicative activities and decreased aphasia severity
D'hooghe et al. (81)	MS [*N* = 57]	Relapsing-remitting MS with Expanded Disability Status Scale ≤ 4	[57 vs. –]	No	A combination of self-management and motivational messages, to enhance self-energy management and physical activity to improve the level of fatigue in pwMS	Modified Fatigue Impact Scale (MFIS) Short Form-36 (SF-36) Hospital Anxiety Depression Scale (HADS)	MS TeleCoach is a potential self-management tool to increase activity and reduce fatigue
Dennett et al. (82)	MS [*N* = 135]	Unspecified	[90 vs. 45]	Conventional home (paper format)	Web-based exercises with personal conversational support through the weekly interviews	Interviews	The web-based physio is important for building in conversations with people with MS about expectations of exercise and its potential benefits, particularly for those whose condition is deteriorating
Vries et al. (83)	PD [*N* = 16]	Unspecified	[16 vs. –]	No	Video recorded movement observation.	Semi-structured interviews after the software exposure	The following conditions were identified to foster patients' engagement: Camera recording (e.g. being able to turn off the camera), privacy protection (e.g. patients' behavior, patients' consent, camera location) and perceived motivation (e.g. contributing to science or clinical practice)
Thomas et al. (84)	MS [*N* = 15]	Unspecified	[15 vs. –]	No	Telephonic interviews	Interviews	Particularly of interest were themes related to replicating the group dynamics and the lack of high-quality solutions that would support the FACETS' weekly homework tasks and symptom monitoring and management

(Continued)

TABLE 3 | Continued

References	Clinical condition [total sample size]	Patients characteristiscs	Case vs. control group [size]	Control group [type]	Case group [type of engagement]	Engagement assessment	Main results
Chemtob et al. (85)	SCI [*N* = 33]	SCI with paraplegia, chronic phase (≥1year postinjury)	[22 vs. 11]	Usual care	The counseling sessions focused on fostering the basic psychological needs and autonomous motivation, teaching behavior change techniques, and self-regulatory strategies	Conversation analyses	The intervention group reported greater autonomous motivation post-intervention. Large to moderate effects supporting the intervention group were found for health participation, and meaningful life experiences and social cognitive predictors. A trained physical activity counselor can increase physical activity motivation
Ellis et al. (86)	PD [*N* = 61]	Mild-to-moderate stage (Hoehn and Yahr score 1–3)	[44 vs. 21]	Active control group	Cognitive-behavioral elements to enhance the basic behavioral change component of the individualized exercise and walking program and to emphasize participants' engagement in managing their health condition	Daily records of steps taken and exercises performed, using either the mobile health application (mHealth group) or paper calendars (active control group)	Adherence to the exercise program was similar between groups. The addition of enhanced, remotely monitored, mobile technology-based, behavioral change elements to the exercise prescription appeared to benefit participants who were less active differentially

TBI, Traumatic Brain Injury; ABI, Acquired Brain Injury; SCI, Spinal Cord Injury; MS, Multiple Sclerosis; PD, Parkinson disease; LSS, Lumbar spinal stenosis.

TABLE 4 | TiDER checklist study characteristics.

References	Brief name	Aim	Set-up	Task	Who provided	How	Where	When/How much	Tailored	Intervention adherence
Yeh et al. (69)	Motivation and Telerehabilitation	To provide a telerehabilitation experience to create an elevated mood state allowing patients and therapists to experience a sense of co-presence that will be associated with satisfaction with the telerehabilitation system, and willingness to persist in therapy	A telerehabilitation system composed of two subsystems: a motor rehabilitation system, and a tele-communication system	The therapists had to guide the patient through the setup of the systems and then talk him/her through three computer games designed to provide motor rehabilitation exercises for the upper extremity	Therapist (Unspecified role)	Remotely from placed at a different location through the telerehabilitation system	Therapist/patient pairs were taken into separate rooms.	Daily therapy during an unspecified time	The difficulty levels and the progress in gameplay were monitored and manipulated through a live video chat during the exercise	Two 7-point scale items measured daily therapy during an unspecified time the willingness to persist in therapy
Lloréns et al. (70)	Virtual reality for self-awareness	To study the effectiveness of the virtual system in the rehabilitation of self-awareness skills	A multi-touch non-immersive virtual reality system	Patients had to move forward in the virtual game by answering questions, which can be related to knowledge (anatomical and pathological matters, red cards), reasoning (situational exercises, blue cards), action (role-playing exercises, green cards), or cohesion (jokes and sayings, yellow cards), related to their clinical condition	Self-provided by the patients	Self-provided by the patients at hospital	At hospital	1-hour session per week during 8 months	No	No
White et al. (71)	Tablet acceptability in stroke survivors'	To explore stroke survivor acceptability of and experience of tablet use during the first three months of stroke recovery	Tablet technology	A qualitative study using an inductive thematic approach incorporating the process of constant comparison was utilized to collect and analyze data	Self-provided by the patients	Remotely	Patients' home	During the first three months of stroke recovery	Not specified	Qualitative outcomes were participants' perceptions using in-depth, semi-structured interviews
Ferreira et al. (72)	Teleassessement in pwPD	To assess the feasibility and usability of an objective, continuous, and relatively unobtrusive system (SENSE-PARK System	SENSE-PARK System which consists of wearable sensors, a smartphone-based App, a balance board, and computer software	To perform a balance and cognitive training	Two trained researchers were involved. The training was administered by the SENSE-PARK System	Remotely	Patients' home	Sensors' information was registered 24 hours/7 days over 12 weeks	Not specified	Semi-structured interviews were conducted by phone to gain insight into the experiences of the participants using the SENSE-PARK System. Topics discussed were: willingness to continue in the study, satisfaction with the SENSE-PARK System, changes in health status or medical condition, adverse events, feedback messages, and doubts about the system

(Continued)

TABLE 4 | Continued

References	Brief name	Aim	Set-up	Task	Who provided	How	Where	When/How much	Tailored	Intervention adherence
Nijenhuis et al. (73)	A motivational self-administered training for stroke	To assess the feasibility and potential clinical changes associated with a technology-supported arm and hand training system at home for patients with chronic stroke	A computer containing user interface and games, Touchscreen and SaeboMAS, SCRIPT wrist and hand orthosis	To perform an upper limb training combining assisted movement by an orthosis and motor videogame	Trained clinical researchers (human movement scientists), physical therapists, or occupational therapists remotely	Remotely	Patients' home	30 minutes of exercise per day, 6 days per week	Game difficulty schedule was used by the HCP weekly to provide the correct game categories to each participant. The HCP adjusted the training program remotely by accessing the HCP user interface	The System Usability Scale is a 10-item scale to assess a global view of the subjective experience of system usability
Lloréns et al. (74)	Telerehabilitation of balance after stroke	To evaluate the clinical effectiveness of a virtual reality-based telerehabilitation program in recovering balance compared to an in-clinic program in hemiparetic patients with stroke. Second, to compare the subjective experiences, and finally, to contrast the costs	The hardware system consisted of a TV, a standard computer, and a Kinect™ (Microsoft®, WA). A 42" LCD screen and a PC were used in the clinical setting	The VE used in the experiment represented the participants' feet and their movements in an empty scenario, which consisted of a checkered floor that facilitated the depth perception, with a central circle that represented the center of the VE. Different items rose from the floor around the circle	Two physical therapists were involved remotely to detect possible issues and act accordingly	Remotely	Patients' home	45-minute training sessions, 3 days a week, during 8 weeks.	The level of difficulty of the task was defined by configuring the region of appearance, distance, size, lifetime, and number of simultaneous items. The difficulty of the task was adjusted automatically by the system	The System Usability Scale is a 10-item scale to assess a global view of the subjective experience of system usability
Palacios-Ceña et al. (75)	Kinect VR home-based program in pwMS	To explore the experiences of multiple sclerosis patients who performed a virtual home-exercise program using Kinect	Kinect home-exercise program	Postural control and balance exercises	Medical doctors and therapists were involved in the recruitment and assessment times	Remotely	Patients' home	10-week training	Unspecified	Unstructured interviews, using open questions, and thematic analysis were conducted
Houlihan et al. (76)	Enhancing self-management in pwSCI	To evaluate the impact of "My Care My Call" (MCMC), a peer-led, telephone-based health self-management intervention in adults with chronic spinal cord injury (SCI)	Telephone	Trained peer health coaches applied the person-centered health self-management intervention	Trained peer health coaches	Remotely	Patient's home	6 months on a tapered call schedule	Unspecified	Phone interviews
Engelhard et al. (77)	Remotely engagement in MS	To evaluate web-based patient-reported outcome (wbPRO) collection in pwMS in terms of feasibility, reliability, adherence, and subject-perceived benefits; and quantify the impact of MS-related symptoms on perceived well-being	Web portal	Patients had to report symptoms from home and view their symptom history. Subjects were required to complete each of the five questionnaires	Unspecified	Remotely	Patients' home	One per month during 6 months	No	Questionnaires at the web portal

(Continued)

TABLE 4 | Continued

References	Brief name	Aim	Set-up	Task	Who provided	How	Where	When/How much	Tailored	Intervention adherence
D'hooghe et al. (81)	MS Telecoach feasibility	To enhance levels of physical activity, thereby improving fatigue in pwMS in an accessible and interactive way, reinforcing self-management of patients	Smartphone application consisting of two main components: telemonitoring and telecoaching	Patients had to perform a physical activity training while they were telemonitored and telecoached	Unspecified	Remotely	Patient's home	2- week run-in period was followed by a 12-week evaluation period	No	Telemonitored information about physical activity by the smartphone application. Visual analogue scale to assess levels of fatigue
Lai et al. (78)	Telemonitored rehabilitation in pwPD	To explore the uptake and implementation of Tele-Monitored Home-Exercise program in adults with PD	Android computer tablet with Bluetooth and wireless Internet capability, mounted to an adjustable floor stand. A wearable physiologic monitor (BioHarness 3, Zephyr)	Combined strength and aerobic exercise. Participants exercised under a telecoachs' supervision via videoconferencing	Research staff	Remotely	Patients' home	8 weeks of exercise, 3 sessions per week: with a total of 24 sessions	No	Measures of adherence included four variables: (a) the total number of exercise sessions performed, (b) time in minutes exercising per week, (c) time exercising at a moderate aerobic intensity per week, and (d) attendance. Interviews included 10 open-ended questions that served as general prompts for discussion in the following areas: perceptions of the program, equipment/devices, exercise setting, telecoach (or not having one), and rationales for exercise adherence
Skolasky et al. (79)	Improving Rehabilitation Engagement After Spinal Stenosis Surgery	To compare the effectiveness of health behavior change counseling with usual care to improve health outcomes after lumbar spine surgical procedures	Telephone	Health behavior change counseling is a brief, telephone-based intervention intended to increase rehabilitation engagement through motivational interviewing strategies that elicit and strengthen motivation for change	Clinical staff	Remotely	Patients' home	Participants were assessed before the surgical procedure and for 3 years after the surgical procedure for pain intensity	No	Phone interviews
Pitt et al. (80)	Telerehabilitation in pw aphasia	To describe changes in aphasia severity, and communication-related QOL and participation, for people with chronic aphasia following TeleGAIN	Web-based videoconferencing	Treatment provided opportunities to participate in a conversation, engage with others with aphasia, and complete functional communication activities	Clinicians and patients	Remotely	Patients' home	12 weeks	No	Communication-related quality of life and participation assessments
Dennett et al. (82)	Web-based physical intervention in pwMS	To explore the experiences of participants who used a web-based physiotherapy intervention as part of a feasibility randomized controlled trial by in-depth interviews	Web-based exercise platform	Patients had to perform a web- based exercise program	Physical therapist	Remotely	Patients' home	Twice-weekly web-based physiotherapy sessions.	No	Interviews were audio-recorded, transcribed verbatim, and analyzed using thematic analysis

(Continued)

TABLE 4 | Continued

References	Brief name	Aim	Set-up	Task	Who provided	How	Where	When/How much	Tailored	Intervention adherence
Vries et al. (83)	Home-based video intervention in pwPD	To study the barriers and facilitators as perceived by PD patients considering continuous video recording at home for medical research and/or medical treatment purposes	Home-based video system + Kinect camera, which measures motor functioning	Patients had to perform their motor training routine, and it was recorded through the Kinect to the assessment of movement parameters, including standing up and several gait parameters	Research staff	Remotely	Patients' home	Motor training: not specified Interviews were conducted during 1 year	No	Interviews were semi-structured and included a standardized introduction, open-ended questions, and prompts to encourage further discussion and more specific answers
Thomas et al. (84)	Digital fatigue management in pwMS	To gather views about a web-based model of service delivery from HCPs who had delivered FACETS and from pwMS who had attended FACETS	Telephone	Telephone consultations were undertaken with FACETS-trained HCPs who had the experience of delivering FACETS	Clinicians	Remotely	Patients' home	Face to face consultation intervention	No	Interviews
Chemtob et al. (85)	Telehealth to enhance motivation in pwSCI	To test a pilot tele-health intervention, grounded in self-determination theory, to enhance need satisfaction, motivation, physical activity, and quality of life among adults with SCI.	Online video-chat platform.	Patients had to perform a leisure-time physical activity program that has been supported by an online coach intervention	Psychologist	Remotely	Patients' home	The Intervention group received online 1hour of counseling session per week, during 8 weeks	No	Online counseling
Ellis et al. (86)	Effectiveness of mHealth in pwPD	To explore the preliminary effectiveness, safety, and acceptability of a mobile health (mHealth)–a mediated exercise program designed to promote sustained physical activity in people with PD	Mobile health (mHealth)	Patients had to perform a mobile health–mediated exercise program ("mHealth" condition) with an exercise program administered without mobile health technology	Unspecified	Remotely	Patients' home	12-month single-blind (assessor)	No	Exercise adherence data were collected via daily records of steps taken and exercises performed, using either the mobile health application. Program acceptability was assessed after 12 months by having participants rate their satisfaction using a 1 to 10 Likert scale

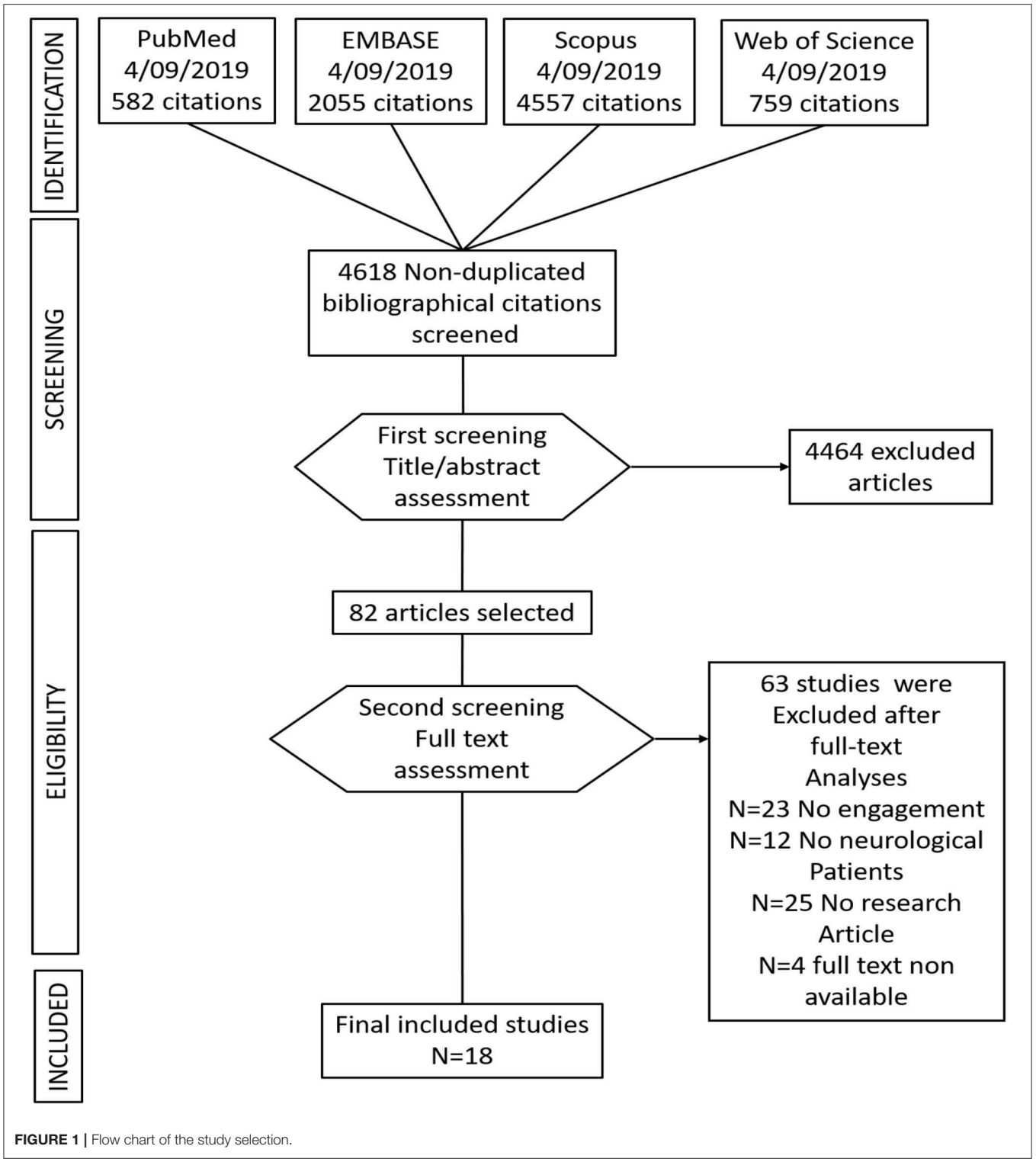

FIGURE 1 | Flow chart of the study selection.

measure for engagement assessment (71, 75, 83–85). All the studies included in this review reported their allocation sample method and study design. However, 12 studies did not have used random allocation methods for the sample allocation and not included a control group in the study design (70).

Engagement Interventions in Teleneurorehabilitation

Once the final 18 studies included in this systematic review have been analyzed, the studies were divided in those in which engagement was considered a primary outcome of the

telerehabilitation training ($n = 11$) (70–72, 76–79, 81, 82, 84, 85), and those in which engagement was considered a secondary outcome of the telerehabilitation training ($n = 7$) (69, 73–75, 80, 83, 86).

Engagement as a Primary Outcome

Most of the 11 analyzed studies aimed at investigating the patient engagement as a primary outcome through a telerehabilitation training in patients with neurological disorders. In specific those studies involving patients' self-management, self-awareness, and self-determination strategies to enhance active patients' participation in their healthcare routine, and providing patients' empowerment. Such engagement strategies have been included in the behavioral and cognitive dimension of engagement (88). Specifically, in the present systematic review, four studies directed to enhance the behavioral and cognitive dimension of engagement while using telerehabilitation systems have been found. For instance, a non-immersive virtual reality multitouch system had been used in 10 acquired brain injury patients (ABI) at home to treat self-awareness deficit (70). Particularly, patients were engaged in a self-awareness game consisting of answering questions related to knowledge (anatomical and pathological matters), reasoning (situational exercises), action (role-playing), or cohesion (jokes and sayings), in a competitive context (70). Further, in another study, the authors used a smartphone application for both the telemonitoring and tele-coaching of 57 patients with multiple sclerosis (MS) (81). The study by D'hooghe et al. aimed at fostering patients' self-energy management and physical activity, decreasing the level of fatigue after physical activity. Regarding patients with MS, a web-based model (FACETS: Fatigue: Applying Cognitive-behavioral and Energy effectiveness Techniques to life Style) of service delivery from healthcare providers was also tested in 15 patients with MS to improve patients' behavioral and cognitive dimension of engagement (84). Further, an online video-chat platform was used as a pilot test telehealth intervention, grounded in self-determination theory, to enhance satisfaction, motivation, physical activity, and quality of life in adults with spinal cord injury (SCI) ($n = 11$) (85). Finally, an android application in a tablet together with a physiologic monitor was used as a telehealth system in 20 patients with PD to explore two different internet engagement trainings: a tele-coach assisted training ($n = 10$), and a self-regulated exercise training ($n = 10$) (78).

Other frequent strategies used for engagement in telerehabilitation are those directed to enhance patients' adherence and compliance to the therapy. Concerning this, in this systematic review, one study used a mobile web portal (wbPRO) to evaluate patient-reported outcomes in terms of feasibility, reliability, adherence, and subject-perceived benefits in 31 patients with MS, to quantify the impact of MS-related symptoms on the perceived patients' well-being (77). Moreover, a more sophisticated telerehabilitation system (SENSE-PARK system) including a set of wearable sensors (three to be used during the day and one at night), a Wii Balance Board software, and a smartphone application was used at patients' home to assess the feasibility and usability of the system, in 22 patients with PD (72). Further, a web-based physiotherapy platform with weekly personal, conversational support was used in patients with MS ($n = 45$), compared to a usual home paper format protocol ($n = 45$) to explore the user experience and feasibility of a web-based intervention (82).

Finally, in this systematic review, two studies directed to investigate the emotional components of the engagement strategies when using telerehabilitation systems were also found. These types of engagement strategies are embedded into the emotional dimension of engagement (88), usually implemented by using telephone and email interviews. Particularly, two studies were directed to enhance the emotional dimensions of engagement (76, 79). Specifically, in the study conducted by Houlihan et al., the therapists assessed the results obtained from a telephone-based health self-management intervention in patients with SCI ($n = 42$), compared with a usual care control group ($n = 42$). However, in the study conducted by Skolasky et al., the clinical staff involved in the study used motivational interviewing strategies to elicit and strengthen motivation for change in patients with MS ($n = 31$).

Engagement as a Secondary Outcome

Seven studies of this systematic review aimed to use telerehabilitation training for motor, cognitive, or logopedic interventions in patients with neurological disorders and to enhance patient engagement as a secondary outcome. Specifically, in this review, three studies were directed to investigate user experience, and system feasibility when using telerehabilitation systems for other neurorehabilitation proposes (73, 83, 86). As an example, in the study conducted by Ellis et al., they explored the preliminary effectiveness, safety, and acceptance of a mobile health (mHealth) application–a mediated exercise program– designed to promote sustained physical activity in 23 patients with PD. Moreover, in another study, the authors assessed the feasibility and potential clinical changes associated with telerehabilitation training for upper limb recovery, based in a robotic technology-supported arm, supported by a video-game training system in 24 patients with chronic stroke (73). Finally, De Vries et al. reported the opinion of 16 patients with PD when using a home-based system without video movement analysis (83).

Moreover, the other five studies aimed at investigating engagement as a secondary outcome when using telerehabilitation systems for neurorehabilitation proposes. Specifically, one study investigated changes in aphasia severity, communication-related quality of life, and participation, in 19 patients with aphasia while using the TeleGAIN telerehabilitation system (80). Moreover, another study investigated postural control and balance improvements after a 10-week of a virtual Kinect home-exercise program in 24 adults with MS, and assessed patients' adherence and motivation when using the telerehabilitation system as a secondary outcome (75). In one study conducted by Yeh et al., the authors tested a telerehabilitation system composed of two subsystems: a motor rehabilitation system and a telecommunication system to improve the mobility of patients with stroke and to motivate them to continue with the telerehabilitation training (69).

Finally, in another study, the effectiveness of a virtual reality-based telerehabilitation program for balance recovery in chronic stroke patients was assessed and compared to the usual rehabilitation training (74).

Engagement Assessment

Among the analyzed studies in this systematic review, the following main three assessment methods have been found to assess patient engagement: measurement scales, telephone based-interviews, and paper diaries. Regarding the measurement scales in the study conducted by Lloréns et al. (70), the authors used the Self-Awareness Deficits Interview (SADI) scale (89), and the Social Skills Scale (SSS) (90). However, others used the Short Form-36 (SF-36) (91), and the Hospital Anxiety Depression Scale (HADS) (92) to assess engagement as a secondary outcome (81). Moreover, the Communication Life Scale and the communicative activities checklist were used in patients with aphasia to assess engagement as a secondary outcome (80). Finally, three scales directed to assess engagement as a primary outcome were used. The Intrinsic Motivation Inventory (IMI) (93), was used to assess the level of motivation in patients with stroke after the telerehabilitation period (73). The Patients Activation Measure (PAM) (23), was used to assess health self-management in patients with SCI (76). Finally, the Profile of Mood States (POMS) questionnaire (94) was used in patients with SCI or ABI after the telerehabilitation training period (69). **Table 5** aims to summarize the different scale measures, and the aim of each engagement scale measure.

Engagement Outcomes

Engagement as a Primary Outcome

Regarding the outcomes observed in the analyzed studies which aimed to foster patient engagement as a primary outcome, we observed the following reported outcomes. The VR game proposed in the study conducted by Llorens et al., improved self-awareness and social cognition deficits in patients with ABI and PD after 8 months of a telerehabilitation training (70). Through a smartphone TeleCoach application, patients with MS increased activity and reduced fatigue levels after 12 weeks of training, improving patients' self-management (81). Moreover, another study demonstrated that by replicating rehabilitation group dynamics through a telerehabilitation system is possible to enhance patient engagement to the rehabilitation training in patients with MS (84). Regarding the use of telerehabilitation training in patients with stroke, one study showed that by using an iPad training stroke survivors experienced increased participation in therapeutic activities, increased socialization, as well as less inactivity and boredom (71). In addition to this, the results obtained in the study conducted by Nijenhuis et al. showed an increased motivation to participate in the rehabilitation training when using a remotely monitored training system at home (73). However, in another study conducted in patients with PD, the patients reported that direct feedback about the patients' health condition when using the telerehabilitation training system would help to increase patients' motivation (72). Another study showed that patients with PD benefit from a mobile biofeedback system that provides real feedback about patients' health conditions, and enhance patient engagement to the rehabilitation routine (86). Furthermore, in one study in which patients with stroke could feeling the sense of the co-presence of the therapist during the telerehabilitation training, the psychological state of the patients was improved (69). However, in contrast to the above-commented studies, one study reported a reduction in patients' self-efficacy and willingness regardless of patients' fatigue after the telerehabilitation training (69).

Finally, one study highlighted the importance of building in conversations by weekly interviews with people with MS about expectations of exercise and its potential benefits, particularly with those patients whose physical and mental conditions may be deteriorating while using motor telerehabilitation systems (82). In this regard, another study reported that health behavior change counseling by telephone-based interventions could improve health outcomes during the first 12 months after the surgical procedure in patients operated of spinal stenosis, improving patient engagement to the rehabilitation program (79). Moreover, 6 months of a telerehabilitation period based in a telephonic intervention program showed a more significant change in PAM scores, as well as a higher decrease in social/role activity limitations, and improvements in services/resources awareness in patients with SCI (76). Further, another telerehabilitation training using an online video-chat platform increase autonomous motivation in patients with SCI (85).

Engagement as a Secondary Outcome

Regarding the outcomes observed in the analyzed studies which aimed to foster patient engagement as a secondary outcome, we observed the following reported outcomes. One study reported improvements in communication-related quality of life in patients with aphasia, and a decrease of the aphasia severity, which lead to an increase of patient engagement in communicative activities (80). Another study conducted by Palacios-Ceña et al. highlighted the following positive factors reported by patients with MS after using a Kinect telerehabilitation systems: (1) the Kinect training increased the level of independence of the patients; (2) the patients reported to can share their illness state with their relatives'; (3) the patients reported positive effects about the incorporation of a videogame for rehabilitation, and (4) the patients reported positive effects regarding the possibility of evaluating themselves through the feedback provided by the telerehabilitation system (75).

Engagement Strategies Effectiveness

Overall, we found different patient engagement strategies throughout the 18 analyzed studies. **Table 6** summarizes the different engagement strategies found among the analyzed studies, and the level of effectiveness of such engagement strategies for teleneurorehabilitation (positive, neutral, or negative). Specifically, 12 studies reported positive results when using tele-neurorehabilitation interventions for patient engagement (69, 70, 73, 75, 76, 78–83, 85). Five studies reported neutral effects in patient engagement after the tele-neurorehabilitation training period (71, 72, 74, 84, 86).

TABLE 5 | Summary of engagement scale measures.

Engagement scale measures	Type	Aim
Self-Awareness Deficits Interview (SADI) scale (89)	An interviewer-rated, semi-structured interview	To obtain both qualitative and quantitative data on the status of self-awareness following TBI. The interview has three areas of questions: (1) self-awareness of deficits; (2) self-awareness of functional implications of deficits; and (3) ability to set realistic goals
Intrinsic Motivation Inventory (IMI) (93)	Short- or long-form questionnaire	To measure grounded on the Self-Determination Theory (SDT) used in assessing the subjective experiences of participants when developing an activity. Specifically, it evaluates interest and enjoyment in a task, along with several other factors
Patients Activation Measure (PAM) (23)	A valid, highly reliable, unidimensional, probabilistic Guttman-like scale	To reflect a developmental model of activation, by assessing four different stages in patients activation: (1) believing the patient role is important, (2) having the confidence and knowledge necessary to take action, (3) taking action to maintain and improve one's health, and (4) staying the course even under stress
Profile Of Mood States (POMS) questionnaire (94)	A long (65 items) or short (35 items) questionnaires that contain a series of descriptive words/statements that describe feelings people have. The subjects self-report on each of these areas using a 5-point Likert scale	To measure peoples' mood state

TABLE 6 | Summary of engagement variables in tele-neurorehabilitation and engagement improvement.

Included studies	Self-awareness/ Self-management	Adherence to the intervention/Satisfaction	Emotional support	Patient activation/motivation	Engagement improvement
Yeh et al. (69)		X	X		Positive
Lloréns et al. (70)	X				Positive
White et al. (71)		X	X	X	Neutral
Ferreira et al. (72)		X		X	Neutral
Nijenhuis et al. (73)		X		X	Positive
Lloréns et al. (74)		X		X	Neutral
Palacios-Ceña et al. (75)		X		X	Positive
Houlihan et al. (76)	X	X	X	X	Positive
Engelhard et al. (77)	X	X	X		Negative
D'hooghe et al. (81)	X	X	X		Positive
Lai et al. (78)	X	X			Positive
Skolasky et al. (79)		X	X		Positive
Pitt et al. (80)		X		X	Positive
De Vries et al. (83)		X		X	Positive
Dennett et al. (82)		X	X		Positive
Thomas et al. (84)	X	X	X		Neutral
Chemtob et al. (85)		X	X	X	Positive
Ellis et al. (86)		X			Neutral

Finally, only one study out of the 18 analyzed studies reported negative results in patients' adherence to the training after the telerehabilitation training period (77).

DISCUSSION

The engagement of patients in the rehabilitation process is considered a primary aim for worldwide healthcare interventions [see (95)]. Patient engagement is considered a key component in neurorehabilitation in order to promote greater neuroplastic changes and functional outcomes (2). In this concern, digital technologies have been considered as a useful resource for enhancing patients' participation, allowing them to have an active role in their healthcare process (96, 97). The introduction of digital technologies in the field of neurorehabilitation has prompted the possibility to conduct the rehabilitation protocol at patients' homes (16, 98). Thus, telerehabilitation protocols save time for the patient by reducing displacements to the hospital, and the clinicians can follow the patients after the hospital discharge from the hospital (16, 98). However, which is the

role of engagement when using tele-rehabilitation systems in neurorehabilitation? The here presented systematic review aims at reviewing the different engagement strategies and different engagement assessments while using telerehabilitation systems for neurorehabilitation.

In this systematic review, the studies were first divided into those in which patients' engagement was considered a first outcome of the telerehabilitation training, and those in which engagement was considered a secondary outcome of the telerehabilitation training. Interestingly, more studies that considered patients engagement as a primary outcome of the telerehabilitation training ($N = 11$), compared to those that considered patients engagement as a secondary outcome ($N = 7$) were found. Particularly, most of the analyzed studies that were directed to enhance patients' engagement through telerehabilitation systems in neurorehabilitation, had been conducted during the last 4 years from 2015 to 2019 (70–72, 76–79, 81, 82, 84, 85). This data indicates that fostering patients' engagement through the use of new technologies in neurorehabilitation has been a matter of interest for several years. Interestingly, this data is in line with the systematic review conducted by Barello et al. (99), in which they looked for studies using e-Health interventions for patient engagement, and highlighted the necessity of conducting more studies investigating the use of new digital technologies to enhance patient engagement. The data collected in this systematic review confirms that there was a progressive increase in the use of new technologies to engage patients, specifically those with neurological disorders, into their rehabilitation process. Secondly, our results showed an increase in interest in creating new telerehabilitation protocols in neurorehabilitation for enhancing patients' engagement by promoting patients' self-awareness and self-management ($N = 6$), patients' motivation ($N = 9$), and emotional support ($N = 9$). Such engagement components have been described as components of the behavioral and cognitive dimension of patients' engagement (30). Thus, in this systematic review, the studies analyzed were directed at fostering the behavioral and cognitive dimension through the use of telerehabilitation systems in patients with neurological diseases. These findings are supported by other investigations that were also directed at fostering the behavioral and cognitive dimension of engagement during the rehabilitation process of different clinical populations (100, 101). Concerning this, the results of this systematic review show that the use of telerehabilitation systems in patients with neurological disorders are useful for fostering the behavioral and cognitive dimension of engagement and for increase patients engagement with the rehabilitation program (73, 77, 78, 81, 84, 86). One explanation of this could be that through the telerehabilitation systems it is possible to give a real feedback to the patients about their physical and physiological conditions, as well as the possibility to interact with the telerehabilitation system (70, 73–75, 78, 81, 83). Concerning this, the studies of this systematic review are consistent with later investigations that demonstrated the effectiveness of digital technologies in inducing behavioral, physiological, and emotional responses by giving an immediate real feedback about such responses to the patients (22, 102–104). Moreover, such investigations were also directed at fostering the emotional dimension of the engagement, referring to the patients' acceptance of the disease, to an adequate adjustment to their illness (105), and improving the quality of the relationship between clinicians and patients (24). Specifically, in the analyzed studies of this systematic review, the emotional dimension of engagement has been tackled by using weekly telephonic interviews (72, 76, 84), using a face to face communication through on-line digital platforms (78, 80, 85), or by giving positive and motivating messages to the patients during the telerehabilitation training (78, 81).

Regarding the assessment of engagement during the telerehabilitation training in neurorehabilitation, the studies analyzed in this systematic review show that, at the moment, there are few available scales to assess the level of patient engagement and to deeply assess the different components of engagement. However, some available measures providing quantitative data about patient engagement such as the PAM (23), IMI (93), and the SADI (89), and POMS questionnaire (94) scales are available. Out of these four measures scales, the newest and the most used one is the PAM, which, as described in **Table 5**, enables the assessment of the patient activation during their healthcare routine in-depth. Although the PAM seems one of better measures to assess patient engagement, the POMS questionnaire could be an excellent complement to further assess the emotional state of the patients in their daily healthcare routine and during the telerehabilitation period in patients with neurological disease. The SADI is limited to patients with traumatic brain injury, and this limits the use of this scale to assess self-awareness of the illness in patients with other neurological pathologies. Finally, the IMI could be replaced by the PAM, as this is the newest measure that contemplates more aspects of patient activation in comparison to the IMI. Further, the results obtained in the PAM can reflect patient motivation to participate in their healthcare routine. Besides the quantitative engagement measures, a significant amount of studies that use interviews and diary reports for the qualitative assessment of patient engagement when using telerehabilitation systems were found. In this regard, it is known that data from motivational interviews play an essential role in evaluating patient engagement during the rehabilitation period (106, 107). Moreover, the efficacy of using semi-structured interviews to foster patients with chronic illness to participate in their healthcare routine has been demonstrated (108).

Finally, regarding the effectiveness of the engagement strategies used in the analyzed studies of this systematic review, 12 studies out of 18 reported positive outcomes in fostering patient engagement after the telerehabilitation training. In particular, the engagement strategies used in these 12 studies were mainly focused on patient participation, patient decision making, and patient self-management, all of them involved in the behavioral, cognitive, and emotional dimensions of engagement (see **Table 6**). Such positive results are in line with later studies in which a motivational model to foster participation in the neurorehabilitation programs was proposed (109). Moreover, others also

proposed new neurorehabilitation strategies by enhancing patient self-management, self-awareness, and motivation in rehabilitation routines (2). Most of the revised studies in this systematic review presented positive results by enhancing the behavioral, cognitive, and emotional dimensions of patient engagement. However, most of them used a "monomethod" study design, directed at assessing qualitative or quantitative engagement outcomes.

LIMITATIONS

The present systematic review shows the following limitations regarding the standard protocols for systematic reviews: no registration in a public database, a librarian was not included in the bibliographic research stage, and no duplicate and independent searches of the studies were done.

CONCLUSIONS

The studies commented throughout this systematic review pave the way for the design of new telerehabilitation protocols, not only focusing on measuring quantitative or qualitative measures but measuring both of them through a mixed model intervention design (1). The future clinical studies with a mixed model design will provide more abundant data regarding the role of engagement in telerehabilitation, leading to a possibly greater understanding of its underlying components.

DATA AVAILABILITY STATEMENT

All datasets generated for this study are included in the article/supplementary material.

AUTHOR CONTRIBUTIONS

MM-G and OR developed the paper concept. MM-G carried out the bibliographic review, was responsible for the methodology, and wrote the manuscript draft. MM and JM contributed to the drafting of the manuscript. FB, FR, and PM gave bibliographic suggestions and reviewed the manuscript for important intellectual content. GR, FM, and OR supervised the editing and revisions for important intellectual content. All the authors approved the final version of the manuscript for submission.

FUNDING

The study was co-funded by Lombardy Region (Announcement POR-FESR 2014-2020), within the project named Sidera^B (Sistema Integrato DomiciliarE e Riabilitazione Assistita al Benessere).

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

ORIGINAL RESEARCH
published: 22 May 2020
doi: 10.3389/fneur.2020.00400

A Digital Patient Portal for Patients With Multiple Sclerosis

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OPEN ACCESS

Edited by:
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Specialty section:
This article was submitted to Neurorehabilitation, a section of the journal Frontiers in Neurology

Received: 12 December 2019
Accepted: 17 April 2020
Published: 22 May 2020

Citation:
Voigt I, Benedict M, Susky M, Scheplitz T, Frankowitz S, Kern R, Müller O, Schlieter H and Ziemssen T (2020) A Digital Patient Portal for Patients With Multiple Sclerosis. Front. Neurol. 11:400. doi: 10.3389/fneur.2020.00400

Background: Multiple Sclerosis is a chronic inflammatory disease of the central nervous system that requires a complex, differential, and lifelong treatment strategy, which involves high monitoring efforts and the accumulation of numerous medical data. A fast and broad availability of care, as well as patient-relevant data and a stronger integration of patients and participating care providers into the complex treatment process is desirable. The aim of the ERDF-funded project "Integrated Care Portal Multiple Sclerosis" (IBMS) was to develop a pathway-based care model and a corresponding patient portal for MS patients and health care professionals (HCPs) as a digital tool to deliver the care model.

Methods: The patient portal was created according to a patient-centered design approach which involves both the patients' and the professionals' view. Buurmann's five iterative phases were integrated into a design science research process. A problem analysis focusing on functions and user interfaces was conducted through surveys and workshops with MS patients and HCPs. Based on this, the patient portal was refined and a prototype of the portal was implemented using an agile software development strategy.

Results: HCPs and patients already use digital hardware and are open to new technologies. Nevertheless, they desire improved (digital) communication and coordination between care providers. Both groups require a number of functions for the patient portal, which were implemented in the prototype. Usability tests with patients and HCPs are planned to consider whether the portal is deemed as usable, acceptable as well as functional to prepare for any needed ameliorations.

Discussion: After testing the patient portal for usability, acceptability, and functionality, it will most likely be a useful and high-quality electronic health (eHealth) tool for patient management from day care to telerehabilitation. It implements clinical pathways in a manner which is comprehensible for patients. Future developments of the patient portal modules could include additional diseases, the integration of quality management and privacy management tools, and the use of artificial intelligence to personalize treatment strategies.

Keywords: digital technology, eHealth, patient engagement, patient portals, clinical pathway, neurological disease, chronic disease, multiple sclerosis

INTRODUCTION

Multiple Sclerosis (MS) is a chronic inflammatory, neurodegenerative disease of the central nervous system which leads to a wide range of neurological deficits. It is typically diagnosed in young adult patients between the ages of 20 and 40, and, for the most part, it initially follows a relapsing course. The highly individual symptoms often include fatigue, visual and bladder disorders, pain, spasticity, mobility, and sexual restrictions, as well as psychological disorders such as depression (1, 2), which is why it is popularly referred to as the "disease of a thousand faces" (3). MS patients therefore need to be treated by multi-professional, inter-institutional, and cross-sectoral health care teams, e.g., MS specialists, neurologists, and general practitioners as well as specific specialists and therapists (4, 5). The often decades-long, unpredictable disease course requires ongoing and long-term monitoring, assessment, and management, preferably with digital applications for health care professionals (HCPs) as well as patients (6, 7).

Digital applications are part of the digital transformation in healthcare, which will see the integration of technologies such as advanced analytics, machine learning, and artificial intelligence (8). Digital transformation in healthcare can lead to improvements in diagnosis, prevention, and therapy. It enables HCPs to apply an evidence-based approach to improve clinical decision-making (8, 9). Further examples are the provision of comprehensive information and the rapid exchange of reports and information between patients, experts, and medical centers. Especially in the case of complex, unpredictable, and chronically progressive diseases such as MS, digitalization and electronic health (eHealth) systems can help to better diagnose, monitor, and thus optimally treat individual patients (6).

In the context of improving the treatment of patients, concepts of patient-centered care and shared decision-making must also be mentioned as features of a high-quality health care (10). The Institute of Medicine defines patient-centered care as: "Providing care that is respectful of, and responsive to, individual patient preferences, needs and values, and ensuring that patient values guide all clinical decisions" (11). Patients involved in the treatment process show higher treatment adherence and better treatment outcomes (12–14). In contrast to a role of patients limited to a period of time, chronically ill patients (including MS patients) must play a greater role in shaping their treatment and become experts of their individual care (14, 15). The mostly younger MS patients have a high digital affinity and a high competence in the indexing and use of eHealth services to promote their own patient competence (16–20). To make involvement possible, patients should have access to, as well as understanding of, their treatment plans and context-sensitive information concerning their health status. This means explaining to the patient in a way that is easy for the layperson to understand which treatment steps are being carried out including why, when, and how with regards to their particular phase of illness. Through this, patients get involved in their treatment process and thus, become co-deciders of their treatment. The access to such information can be supported by patient-centered health information technologies, such as patient portals (10). Patient portals are increasingly showing their potential as cost-effective methods that can both improve patients' quality of life and serve as useful tools for patient participation (21). They are also ascribed potential for improving the quality of care (22–24). In general, patient portals have been little used in the German health care system for care management and particularly for involvement of patients so far (25). Especially in the area of clinics, they have mostly been used as information kiosks. This provides a more informational approach for patients without requiring their participation.

In our research, a patient portal for MS patients and HCPs is being developed in the course of inter-organizational MS care. It allows the patient to follow the course of treatment and to correspond with service providers based on the course of treatment (26). The authors aim to introduce patient-centered MS care by implementing a pathway-based care model and by using digital technologies. The electronic patient portal provides personalized information technology (IT) assisted clinical pathways (c.f. section Theory) on the basis of a Fast Healthcare Interoperability Resource (FHIR)-based architecture (FHIR is an interoperability standard for sharing data between application systems in healthcare) (26).

This paper describes the conception of the patient portal based on current knowledge of patient portals and clinical pathways, as well as an existing documentation system (Multiple Sclerosis Documentation System, MSDS^{3D}) (27, 28) and a specifically developed MS case record (c.f. section Theory). In order to successfully implement the patient portal, end users' needs and concerns were taken into account (20, 29). Based on a user-centered design approach (30–32) and a patient-centered participatory design process (21, 33), surveys and workshops with MS patients and HCPs were conducted. The results were incorporated into the development of the portal. The paper provides insight into the functional demands of patients as well as HCPs and shows how these demands can be operationalized in a digitalized MS care model. It describes a technological model for a patient portal, which implements this digitalized MS care model.

The portal named "Integrated Multiple Sclerosis Care Portal"—IBMS—was collaboratively developed by HCPs of the Multiple Sclerosis Center at the Carl Gustav Carus University Hospital and developers of the Chair of Wirtschaftsinformatik, especially System Development at the Technical University of Dresden as well as with the help of MedicalSyn GmbH and Carus Consilium GmbH.

THEORY

Patient Portals and Clinical Pathways

Digital patient portals serve as the basis for patient involvement and for the IT support of MS treatment processes. The recommendations of Van den Bulck et al. concerning patient portal design should be mentioned here as examples of the current state of research: they recommend providing a clinical summary to the patient after each visit, secure messaging between patient and provider, the ability to view, download, and transmit personal health record data, patient specific education,

patient reminders for preventative services, and medication reconciliation (10).

Similar to a checklist in the pilot cockpit, these aspects and the diagnostic and therapeutic procedure can be optimized using defined clinical pathways. Clinical pathways are particularly suitable for the seamless care of chronically ill patients across various health sectors. They describe the entire path of patients during care and unite the multidisciplinary setting, the local conditions, and the current state of evidence research (see **Figure 1**). The focus is on the advance planning of concrete steps of action that are linked to temporal or defined changes in condition (26). In this way, clinical pathways define goals and milestones of care and support the joint decision-making of patients and the multidisciplinary care team involved. Furthermore, patients get more clarity as to which phase of the disease they are in and what current disease activity they have. They are put in a position to contribute to the improvement or maintenance of their state of health by comprehensible situation-oriented recommendations for action. This is intended to strengthen patient competence and intensify the HCP-patient relationship without additional effort on the part of the HCP (26).

Moreover, HCPs were supported in the organization and quality management of care. A consensus-based standardized management path to integrated MS care can contribute as a basis for the development of innovative inter-organizational processes (34). A consensus MS path serves not only as a structure for process organization and quality assurance of MS treatment, but also as an instrument for collecting structured multidimensional data on individual cases of MS in order to develop personalized strategies for MS treatment management (35). These pathways serve various purposes within MS care:

1) **MS care coordination:** The representation of a care model can be done by providing graphical models with dynamic aspects (e.g., the flow of the patient) as well as static aspects (e.g., document structures) (36).
2) **Documentation of patient status:** clinical pathways serve as a tool for managing the patient encounters and the documentation of the current patient status.
3) **Development of patient pathways:** clinical pathways are used and transformed into patient pathways based on patient-specific documentation.
4) **Identification of information flows:** clinical pathways are used to identify information flows for implementing necessary technological measures.

Multiple Sclerosis Documentation System MSDS^{3D}

To manage MS care in a high-quality manner, a certain amount of clinical data is necessary. The relevant data needed, e.g., clinical data, laboratory values, results of magnetic resonance imaging (MRI), and questionnaires (37), are gathered, in the project described here, using a disease-specific software: the multidimensional Multiple Sclerosis Documentation System (MSDS^{3D}), which was developed by the eHealth project group at the University Hospital Dresden and has been continued by MedicalSyn GmbH since 2014. MSDS^{3D} supports patients, nurses, and HCPs (38) in carrying out complex processes such as therapy management (39–41) and it forms the control center for the medical care providers across all institutions and sector boundaries. For clinical data acquisition, the personal and individual circumstances of the participating patients are recorded using tablet-based online questionnaires. Interaction with the patients takes place either via online multi-touch systems, e.g., a touch screen or touch pad as an interactive patient terminal, or via mobile devices, e.g., the patient's smartphone (42, 43). In the MSDS^{3D} system, the recorded data is integrated promptly and actively into the individual treatment process of each patient and can be networked according to standardized clinical treatment paths. MSDS^{3D} regularly reminds the treating HCP of important laboratory or image controls that have to be performed for certain immunotherapies in order to generate large drug-specific real world datasets for specific disease-modifying drugs (44–48).

MS Case Record

The portal also integrates a cross-institutional MS case record which can be accessed by various HCPs in MS care and by patients. Case records typically integrate clinical documentation systems and HCP document systems using electronic interfaces. They are commonly used to implement cross-institutional information exchange (49). The advantage of a case record is that, above all, new actors involved in care and treatment gain immediate insight into all relevant patient and treatment data (50). The prerequisite for storing and viewing the data is the patient's consent, which must always be obtained in writing in accordance with the currently applicable data protection regulations (in Europe: GDPR) (47). The electronic MS case record contains all MS-related information on the patient, and it is mostly used by providers for diagnosis and treatment. A central part of a MS case record is the metadata assigned to the containing documents. A comprehensive specification of this data is crucial both for information provision as well as for information retrieval. It harmonizes different terminologies from different participating systems (semantic interoperability). Consequently, it must represent the terminology of the MS care model and has to fit existing standards (e.g., standard value sets for electronic case records). Documents inside the MS case record can be human-readable (e.g., PDF) as well as machine-readable (e.g., Clinical Document Architecture—CDA, FHIR). This dualism enables a staged creation of electronic case records. Projects can start with a defined set of metadata and human-readable documents. Later on, they can introduce higher formalized document standards which also contain machine-readable data.

METHODS

Design

Following existing user-centered design approaches and patient-centered participatory design processes, surveys and workshops were conducted, and prototypes were created (21, 30–33). As a guiding research model, the authors applied the five iterative

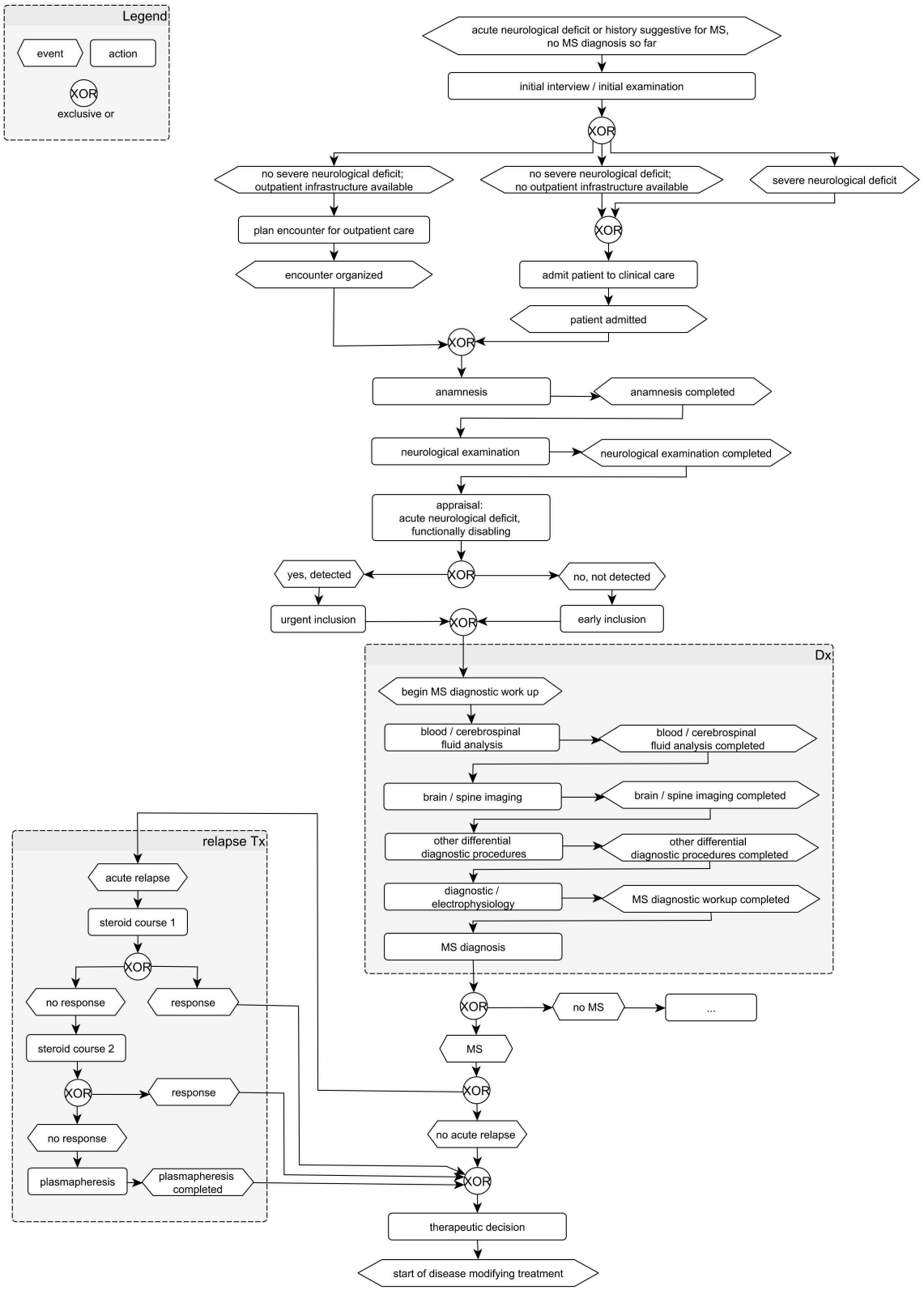

FIGURE 1 | Example for MS pathway model.

phases of Buurmann (32) which were included in a design science research process (51). The phases guided the iterations of the build-evaluate cycle of the design science research process. The authors initially applied surveys in order to get an understanding of the users (phase 1—problem analysis). The electronic portal solution to be developed addresses the needs of the professional and non-professional side equally in the technical context. According to this, the surveys are used to collect technical requirements. In addition, anticipated needs and technical requirements are to be verified in advance. Both aspects serve as input for the technical analysis as well as the subsequent realization. After phase 1, the authors conducted design workshops with HCPs and patients for designing the graphical user interface (phase 2—derivation of functions and user interfaces, phase 3—refinement) and implemented a prototype of the portal based on an agile software development strategy using Scrum (52). A further step, not described in this paper, is the validation of the portal to consider whether it is deemed as usable, acceptable, and functional and as to whether or not it would eventually need ameliorations. After that, the portal can be finalized (phase 4—improvement, phase 5—finalization and operation) (see **Figure 2**). These phases are also operationalized by employing Scrum. Due to the iterative approach, the associated obstacles between the treating HCPs and the patients were also identified with the aim of further improving communication between HCPs and patients in the future.

Procedures: Surveys and Workshops

For the medical concept of the patient portal described here, detailed insights into the treatment process of MS patients were needed. The results of workshops and surveys with HCPs and patients, as well as current findings about the functions of patient portals, were taken into account. It is important to include the requirements of both user groups (MS patients and HCPs), as they have different patient portal demands. Furthermore, they represent the two ends of an information channel. For example, HCPs would certainly like to receive all available clinical information efficiently. Patients may attach more importance to a clear presentation of their examination and treatment appointments. Only by carefully collecting these requirements is it possible to develop a portal that meets the needs of its users and also offers benefits for the providers.

The surveys were not designed as representative surveys from which statements with statistical relevance can be derived. Rather, the surveys had an exploratory character to explore the requirements of patients and HCPs for the patient portal. Consequently, the survey data was analyzed in a purely descriptive manner, no statistical tests of an inductive nature were performed. The results of the workshops were processed and summarized by the project staff.

Prior to the survey and the workshop, each patient was free to withdraw from the survey at any time for any reason without consequences toward the care provided. Because this study involved minimal risk and no personally identifiable information, ethics committee approval was not required.

Patients

Survey (phase 1). A patient survey was partly conducted at an information event for MS patients in 2017. Included were MS patients, relatives, and friends of MS patients as well as people interested in MS. Visitors could inform themselves about the project at an information desk provided. In addition to the presentation of the project's objective and informative discussions, the possibility of voluntary and anonymous participation in a survey was pointed out. If necessary, the background of the survey was explained in more detail. For visitors interested in participating, a total of 200 copies of the questionnaire in paper form were available at the information desk. The participating individuals had the opportunity to process the questionnaire on site or submit it later at the next specialist appointment, by mail or electronically. The response in this manner was 41 questionnaires. The remaining copies were laid out by the University Hospital Dresden in the waiting areas for patients and actively handed out by the study assistants of the Multiple Sclerosis Center. Furthermore, questionnaires were distributed in support groups of the German Multiple Sclerosis Society. A total of 210 questionnaires for the evaluation were thus obtained. The questionnaires were sent directly to the electronic data collection system in an anonymized manner.

The questionnaire consists of five separate parts with a total of 17 questions (thereof four open questions) (see **Supplementary Material**):

1) **Person** (age, MS diseased).
2) **Personal MS** (type of treatment institution, access route, period of MS disease, MS symptoms).
3) **Dealing with information and communication technologies** (use of digital hardware, use for what, use for health, present type of gathering information to MS).
4) **Everyday problems with MS**.
5) **Patient portal** (what use/s should the portal have, requested functions and information).

Workshop (phase 3). Two workshops were conducted in 2019. Included were MS patients and relatives of MS patients interested in using a patient portal; previous knowledge was not necessary. Participants included seven patients and four relatives in the first workshop, and nine patients and one relative in the second. The aim of the workshops was to develop a graphical user interface design based on the input of future users (MS patients and relatives). Requirements were to be developed with the help of different methods (e.g., creative techniques). This was conducted primarily by evaluating previous experiences and user priorities (of the survey). Patients should actively put themselves into possible use cases and evaluate existing concepts accordingly. The workshops were led by two moderators who had experience in the development of medical software as well as expertise in MS.

HCPs

Survey (phase 2). HCPs were asked about their ideas of a patient portal by means of an online survey, which was available from October 2018 to July 2019. Included were MS experts as well as HCPs and nurses who treat MS patients. Four hundred invitations were distributed by mail or e-mail and also given

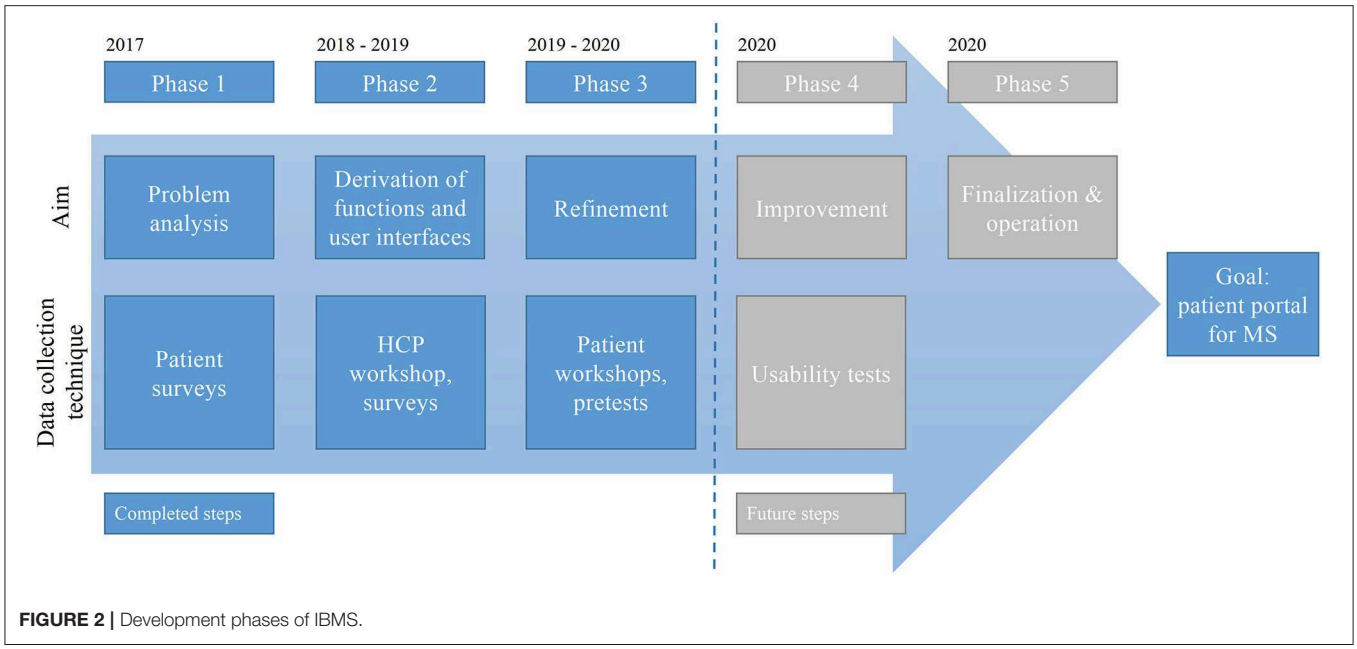

FIGURE 2 | Development phases of IBMS.

to HCPs at congresses and meetings. Participants read and consented to a privacy statement. As an incentive for completing the questionnaire, it was possible to participate in a lottery, for which the participants' data was stored with their consent. The online survey was answered by 22 HCPs and two MS nurses. Only respondents who completed the questionnaire in full were included in the evaluation: after the cleansing of the data set, 16 cases remained including only HCPs and no nurses.

The online survey consisted of 37 questions (with 13 open questions) in five subject areas (see **Supplementary Material**):

1) **Personal information** [e.g., age, years and context of practicing, number of (MS) patients].
2) **System landscape** (e.g., software products for clinicians and licensed HCPs, usage in medical office and networks (MS), content orientation of software, usage of software and hardware).
3) **Treatment of MS patients** (e.g., MS therapeutic methods, ways and frequency of communication with MS patients, contacts to MS patients and other experts, problems in the treatment of MS patients).
4) **Patient portal** (e.g., requested information and functions for MS patients and HCPs, obstacles and risks of usage).
5) **MS case record** [e.g., requested documents and information for a(n) (inter-institutional) MS case record].

Workshop (phase 2). In a workshop held in 2018, the participants (two HCPs and three developers) developed and prioritized portal functions and discussed their graphic representation. The aim was to work out ideas and requirements for a patient portal from the perspective of medical specialists. Functionalities for the patient as well as initial forms of presentation were the focus of discussion. There were no restrictions with regard to the detailing of individual aspects, so that the workshop could be freely designed in the breadth and depth of the discussion.

RESULTS

Surveys and Workshops

Patients

Survey The majority of the 210 participants were themselves affected by MS ($n = 182$). Additionally, 24 MS patients' relatives and friends as well as four individuals interested in MS also took part in the survey. As close confidants and informal care givers, they enriched the survey results with their positions and experiences. The devices commonly used by the 210 interviewed participants are the smartphone and the PC or notebook (see **Figure 3**). The majority of respondents are already using these devices to gather information about their health. One of the main problems of the interviewees in everyday life or in dealing with MS is that available information is not understood. Thus, 90% of the patients stated that they could basically imagine the use of such an electronic portal. Among other things, the insight into the patient report and into important documents, an overview of the drugs to be taken including their purpose and effect, as well as an overview of future visits to the HCP were regarded as helpful functions. In addition, the participants surveyed could imagine the following possible functions: communicating with HCPs via the electronic portal solution, networking with other patients, ordering medication, news and event information, and documenting their course of disease. Besides this, there is a need for information regarding MS disease, its treatment, and disease-specific research, the ability to self-help, coping with everyday life and with the illness, as well as concerns regarding legal and official matters.

Workshop A patient survey, conducted during the workshops, showed that only two of the 16 patients had already used a patient portal. Despite the limited previous experience, the patients and their relatives showed a high level of interest and openness to use a patient portal. The demands of the patients regarding the functionality of the patient portal (see

Figure 3) could be verified in the workshops. As communication-oriented use cases, the patients in the workshops demanded both direct HCP-patient communication and the exchange of information between the care-providers involved in the MS care (e.g., neurologists, general practitioners, and additional therapists). The patients added that documentation sharing between the care provider and the individual should be possible. The graphical visualization of their disease history (symptoms, therapies, treatments) and a diary function (daily documentation of well-being, symptoms, activities, medication) were of great interest. Furthermore, the participants expect to handle administrative procedures such as the application for aids and financial support and to receive information on this issue via the patient portal. The participants await mobile access to their portal data and documents via various devices (e.g., smartphone and tablet). This coincides with the usage of devices resulting from the survey (see **Figure 3**). In addition, they expect the exchange of data with external digital solutions and services (e.g., activity trackers and apps). As the barrier-free nature of the portal plays a key role, due to the impairments of visual performance, concentration, sensitivity, and motor skills that frequently occur in MS patients, alternatives to these digital devices should be provided (e.g., a print function, voice control, user-specific scaling of the user interface). The high relevance of the portal's accessibility was also demonstrated in the handwritten sketches and paper-based wireframes that the participants designed under the guidance of the moderators. The participants prioritized a clear user interface with low information density, intuitive navigation, fold-out tabs for text input or menu selection, input and search fields with default masks, and user-specific settings (e.g., for the information displayed or scaling of the user interface).

TABLE 1 | HCP characteristics.

	***N* = 16**
Age	
18–50 years	7
>51 years	9
Specialist	
Neurologist	12
Double specialist	4
Years of practice	
4–10	1
11–25	9
26–40	4
n. s.	2
Kind of practice	
Licensed	9
Clinic	7
Specialized in MS	
Yes	12
No	4
Proportion of MS patients/quarter	
<50%	5
≥50%	11

HCPs

Survey Even if the survey is not representative (**Table 1**), some interesting aspects can be taken from it; especially since the questionnaire contained many open questions.

For the HCPs in the survey, the use of digital hardware seems to already be part of a daily routine or at least conceivable. They use their software products mostly for settlement, medical documentation, and for the organization of processes and therapies. Apps have not been used much so far. HCPs are connected to the internet and also to healthcare-specific networks like the German "Telematik Infrastruktur." In communication with the patients, the personal conversation has priority, followed by contacts via telephone, mail, and e-mail (see **Figure 4**).

- **Obstacles in patient treatment**: Some HCPs problematize the data protection regulations and the associated complicatedness of the current type of sending reports via encrypted e-mail. Others believe that communication and coordination between care providers is insufficient. It was also mentioned that there is too little time to talk to the patient, that patients do not pass on information to the HCP themselves, and that the information is sometimes incomplete. Individual HCPs would prefer a consultation via video call as some patients have a long way to travel, and they require more support for patients at home.
- **Patient portal**: As a result of the obstacles when treating MS patients, HCPs request a wide range of functions respectively integrated information for a patient portal, mostly general: information for patients regarding disease (industry independent and neutral, in different versions depending on education, in different languages), typical disease courses, therapy monitoring, medication, tools, remedies, complementary measures, socio-medical, and legal matters as well as contacts (MS practices, outpatient departments and clinics, social authorities, self-help groups). HCPs also request an overview of appointments, the therapeutic process, monitoring, and adverse effects for both HCPs as well as patients. They also ask for possibilities for safe digital communication with patients and other HCPs, as well as care providers (e.g., upload findings, import into hospital management system). Overall, the patient portal should always be up to date, should also be usable on mobile devices, and, if applicable, as an app; access and usability should be easy. For HCPs, the highest risk regarding the patient portal is the privacy policy.
- **MS case record**: For the MS case record, HCPs requested all previous and current relevant findings (laboratory, imaging, medical reports, EDSS etc.). Furthermore, it would be desirable to have data from the socio-medical context within the report, e.g., Barthel index, walking distance, degree of care, provision of aids, sick days (due to MS or other), and gainful activity.

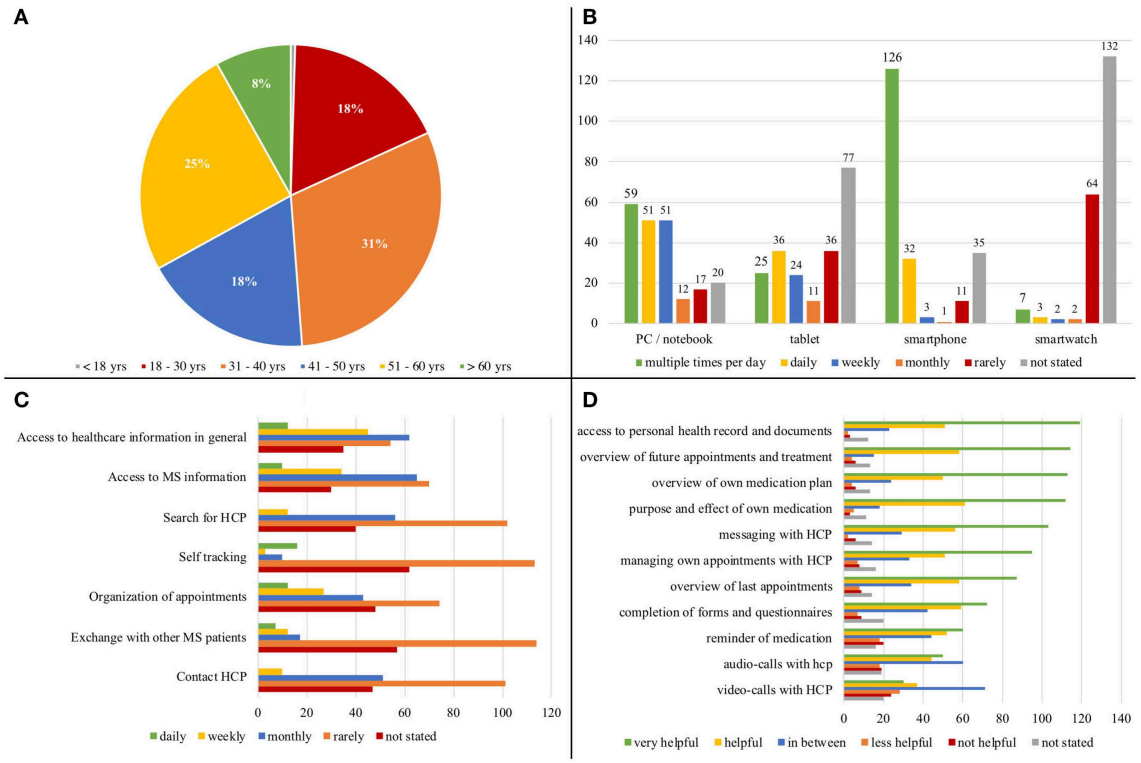

FIGURE 3 | Patient survey participant's… **(A)** age, **(B)** usage of hardware types, **(C)** purpose of technological use, **(D)** assessment of potential portal functions.

Workshop Three topic blocks were discussed and requirements were defined:

- **Access to the portal:** if the patient wishes to use the patient portal, access is granted by the HCP or medical personnel.
- **Dashboard:** The dashboard corresponds to the start page of the portal for the patient after successful login. The following aspects were discussed to be displayed for patients by default: visualized "notification" about (personalized) news about their own health care; and an overview concerning (past and upcoming) appointments, medication, and patient's current tasks ("to dos" e.g., filling out digital questionnaires). For HCPs, the start screen should be designed in such a way that all functions relevant to them can be immediately accessed: a needs-based summary of case and patient information as well as a list of medical "to dos" to be performed during the appointment, graphical presentation of the course of the disease, and the medication process.
- **Functions for patients and HCPs:** In addition to the functions already listed in the dashboard, patients should be able to navigate through a menu to further functions: update profile information as well as store contacts and access rights, view (current and past) medication and request a (follow-up) prescription, view the course of their MS disease in order to track both the temporal occurrence of relapses and changes in course (MS Navigator), view history of MS-related (past and upcoming) appointments, patient-side reporting of illness situation (diary with symptom tracker and pain documentation), and upload or view of medical documents (e.g., MRI, laboratory results, findings, HCP's letters). The medical user should also be able to navigate through a menu to further functions: communication with the patient or consultation with other (MS) experts; view and upload relevant documents; and insight into patient's medication, appointments, and diary.

Construction of the Patient Portal as a Tool for a Patient-Integrated MS Care Model (Phase 3)

Medical Concept

As an organizational framework for digital care provision, a MS care model was developed. The care model consists of organizational structures and processes and references the necessary digital tools. As a process-oriented part, MS specific pathways were developed in the Multiple Sclerosis Center Dresden. These are used as a template for patient-specific pathways that are represented by the patient portal. The MS pathways serve as a conceptual basis for the implementation of the technological patient integration. They are complementary to the organizational structures that are needed to provide inter-organizational MS care. They represent the dynamics of the MS care model (53). The resulting technological solution is a web-based portal which is connected to the existing MSDS^{3D} and a MS case record for access to relevant data. In addition, clinical

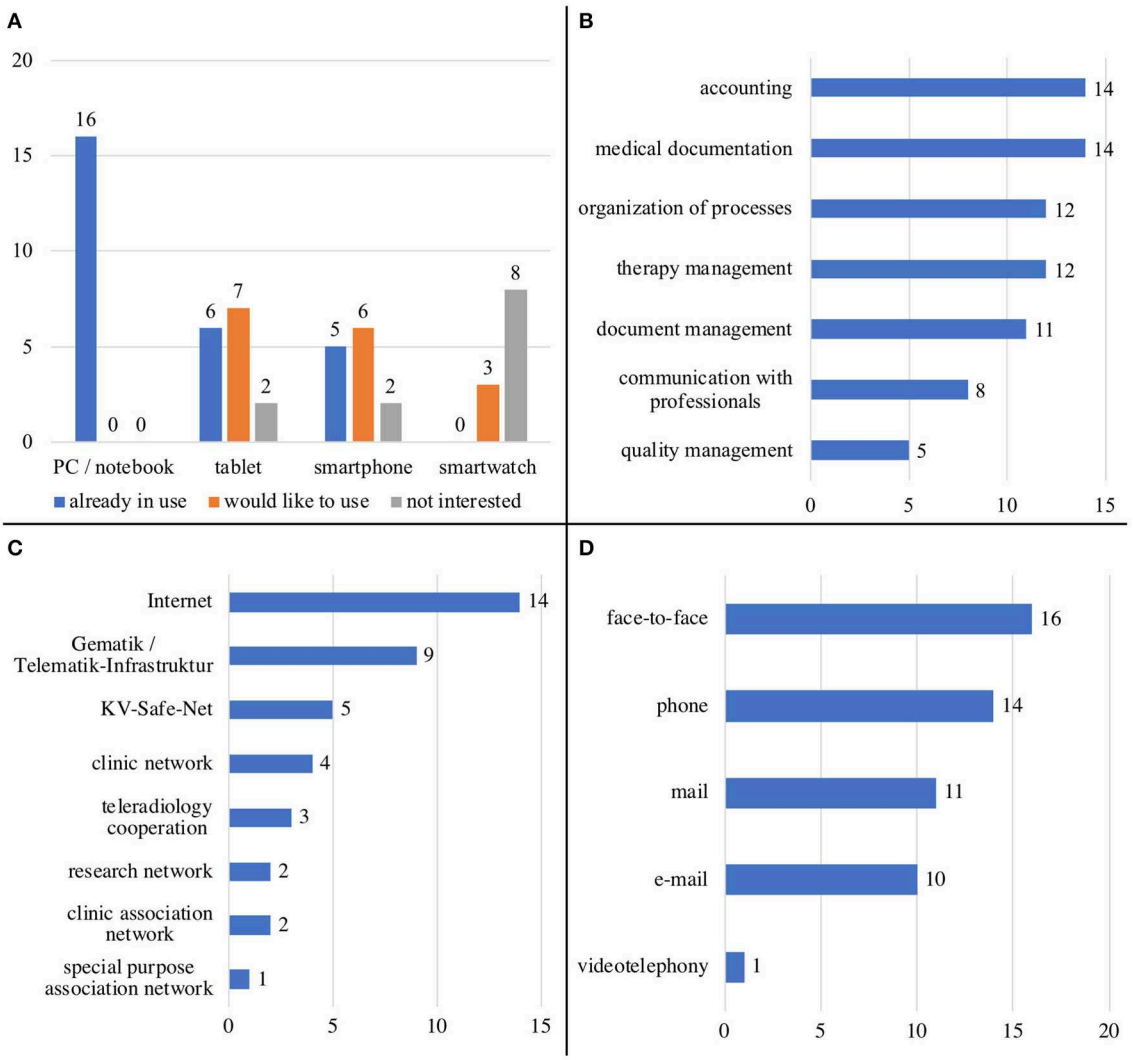

FIGURE 4 | HCP's… **(A)** usage of hardware types, **(B)** usage of software for…, **(C)** connection to…, **(D)** type of HCP-patient-communication.

pathways were operationalized as instruments for MS treatment control and documentation.

Concretely, the patient portal contains a dashboard for patients with news, a MS Navigator to track temporal occurrence of relapses and changes in course (**Figure 5**), MS-related (past and upcoming) appointments, (current and past) medication, current tasks and diary (symptom tracker, pain documentation), as well as access to their MS case record. By integrating a diary, patient reported outcomes (PRO) will be taken into account and can be supplemented later by other factors. For HCPs the start page contains a needs-based summary of case and patient information (MS case record) as well as a list of medical "to dos" to be performed during the appointment, and a graphical presentation of the course of the disease and the medication process.

An example scenario should present the functions of IBMS: Mr. X. visits the neurologist in his place of residence to clarify sudden visual disturbances. His neurologist records the suspicion of MS in MSDS^{3D}. Mr. X. wishes to be registered in the IBMS, is consequently activated for it by his neurologist via MSDS^{3D}, and receives an activation code on site as well as an e-mail with the necessary access information. Via MSDS^{3D} and the central MS case record, the neurologist can also view necessary diagnostic measures and bring in an expert. For diagnostic clarification of the patient's symptoms, MSDS^{3D} is used to arrange and carry out a prompt MRI appointment at the University Hospital. Both the information from the central MS case record and the appointment information as well as the necessary preparatory steps that the patient has to take (e.g., filling out treatment step-related questionnaires) are visible in the timeline of the care portal. Thus, Mr. X. is given the task of filling out a patient admission form in preparation for the examination appointment, which can be done via the IBMS. Following the MRI examination, the data is evaluated by the experts of the University Hospital and the results are reported back to the treating neurologist in real time using the central MS case record. The results

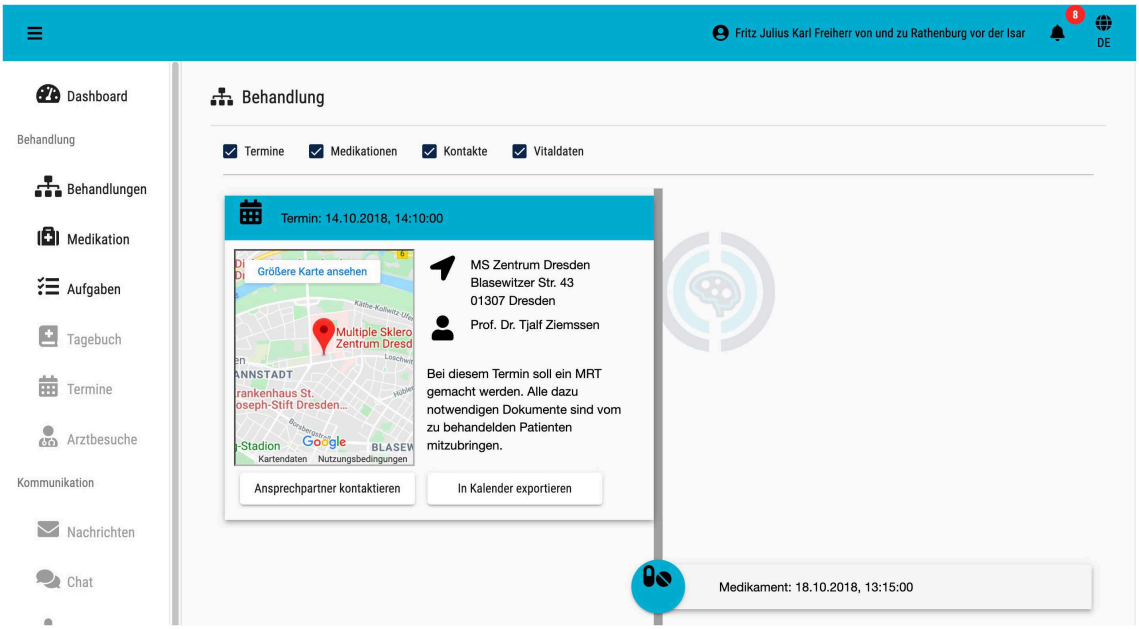

FIGURE 5 | IBMS timeline.

can be transferred to the MSDS^{3D}. Mr. X. then returns to his treating neurologist. The neurologist receives medical data about the networking between MSDS^{3D} and the central MS case record. The information provided via the care portal (e.g., completed questionnaires) is also transmitted to MSDS^{3D}. The experts at the University Hospital can provide the patient with recommendations for action in the form of tasks, information related to the patient-path, and educational materials on the respective path step via the IBMS. Furthermore, the neurologist has the possibility to have a feedback conversation with the expert and to refer to the contents of the central MS case record. Within the IBMS, Mr. X. receives context-sensitive information about his disease. In the process, recommendations for action, made by the experts at the University Hospital, are also taken into account. Mr. X's treatment history can be accessed by a relative if Mr. X grants him the right to do so, which can also be done partially.

Technological Concept

The patient portal for MS care has been implemented by a modular architecture, which is able to include different external systems. Foundational technologies are Angular (angular.io), Java based on a Wildfly-Server (wildfly.org), and other open source technologies (hapifhir.io, postgresql.org). Consequently, the patient portal can be used in different health information system landscapes. Furthermore, a docker-based (docker.com) implementation eases the portability to new information system landscapes.

In order to achieve the flexibility and interoperability, the technological stack is fully based on the HL7 FHIR interoperability standard (hl7.org/fhir/). A first technological configuration has been built by integrating two main systems: the Multiple Sclerosis Documentation System (MSDS^{3D}) and an electronic MS case record (**Figure 6**). The usage of FHIR enables the patient portal to be a highly integrated but independent system. FHIR enables loose coupling and reduces the efforts for bilateral interface negotiation. Furthermore, due to its technological foundation, the Representational State Transfer (REST)-Paradigm, it is of a high platform independency (26).

A module in the patient portal manages the patient pathways and non-pathway data. Pathway information is implemented by HL7 FHIR resources from the Workflow module. The pathways are stored in a pathway repository. The pathway-relevant data is additionally cached in an integrated FHIR server basic pathway information if external systems are temporarily unavailable. The further technological details for pathway-based application systems can be found in Benedict et al. (26). The patient portal and the MSDS^{3D} furthermore implement FHIR resources for task and questionnaire exchange.

The electronic MS case record is integrated by standard IHE XDS.b-interfaces. The XDS.b standard describes how documents can be shared in an inter-organizational setting. The MS case record implements the standard XDS value sets from the German IHE section (http://www.ihe-d.de/projekte/xds-value-sets-fuer-deutschland/). It is extended by MS-specific document types. In order to achieve interoperability, a hierarchical document type approach is used.

DISCUSSION

A patient portal for MS patients and HCPs was developed based on the current knowledge of patient portals and clinical pathways, the existing documentation system MSDS^{3D}, a MS case record, and the investigation of user needs and concerns. Following Buurmann's five iterative phases, which were integrated into a design science research process, a problem

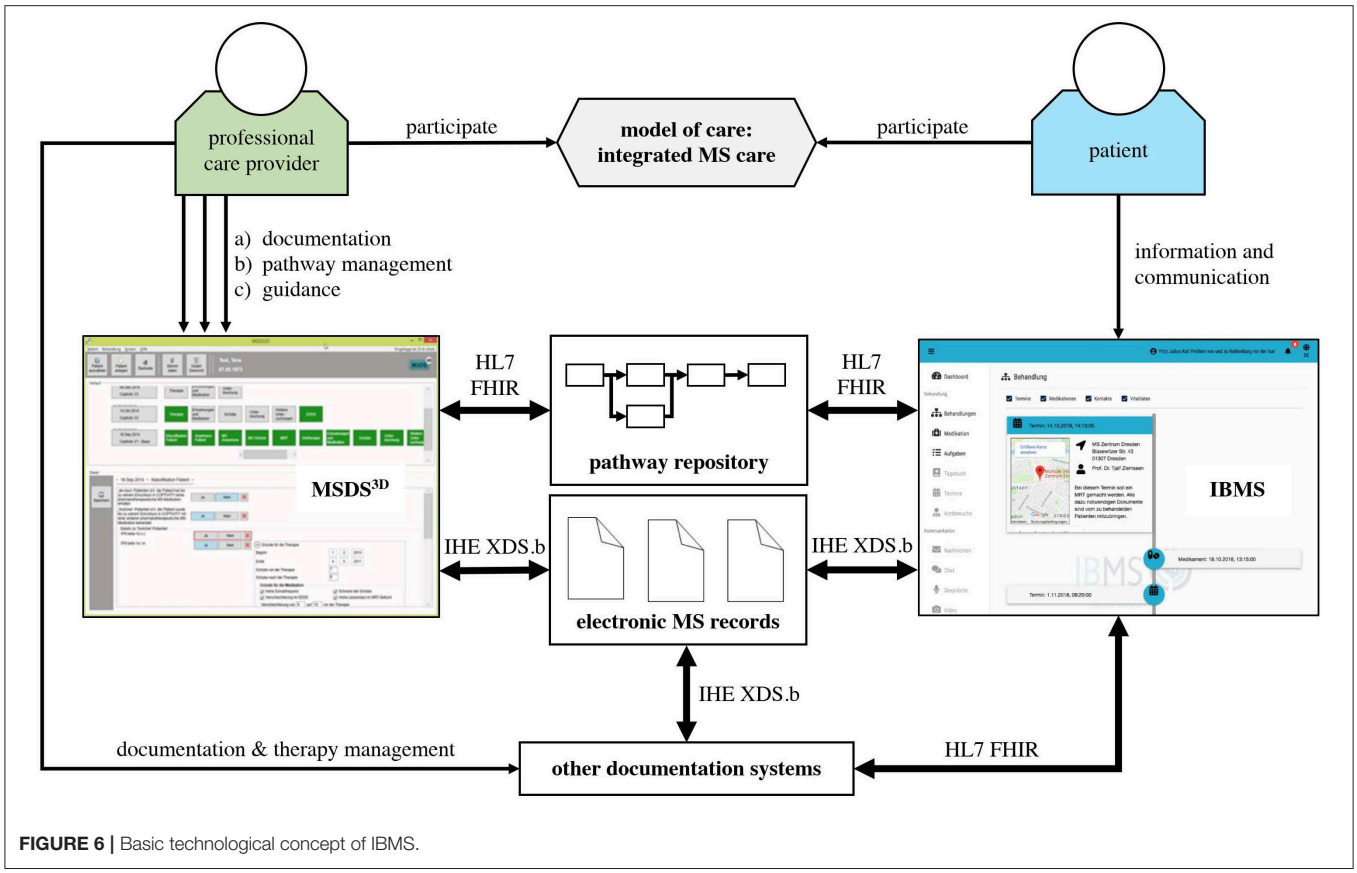

FIGURE 6 | Basic technological concept of IBMS.

analysis was performed focusing on functions and user interfaces through surveys and workshops with MS patients and HCPs. Based on a user-centered design approach and a patient-centered participatory design process, information and requirements on the professional and non-professional side as well as detailed insights into the treatment process of MS patients were collected with surveys (phase 1). Workshops with HCPs and patients were held for discussing the requirements and design of the graphical user interface (phase 2 and 3). The results of the surveys and workshops highlight that HCPs and patients already use digital hardware and are open to new technologies. Nevertheless, an improved (digital) communication and coordination between care providers is desirable. Both groups require a number of functions for the patient portal. Building on this, the patient portal was refined, and authors implemented a prototype of the portal including MSDS^{3D}, an electronic MS case record, and a pathway repository (phase 3). An agile software development strategy was used. A further step, not described here, is the validation of the portal to consider whether it is deemed as usable, acceptable, and functional as well whether it would eventually need ameliorations. Usability tests with patients and HCPs are planned for this (phase 4 and 5).

The innovative digital patient portal has a number of potentially positive impacts for MS patients and their HCPs. It makes decisive contributions to meet the requirements of the enormous diagnostic and therapeutic advances made in neurology. With the help of digital technologies like clinical pathways and case records, the patient portal can help HCPs to better diagnose, monitor long-term, and thus optimally treat individual MS patients. As a result of an optimally adjusted treatment of MS patients, disease progression can be delayed or prevented. Studies using MS-HRS displayed that delaying or preventing disease progression may reduce the societal economic burden of MS (MS-HRS is an easy administrable tool for a holistic assessment of resource utilization from a societal perspective for patients with MS) (54, 55).

The patient portal also offers enormous potential for MS patients, as they face increased challenges from long-term interventions (20). By using the patient portal, MS patients promote their competence and get involved in their treatment process. This can increase the continuity of care and the endurance of MS patients during treatment, as has been seen in other studies (33, 56). Many patients with MS are unable to access health care services for mobility restrictions or lack of locally available health services. The resulting possibilities for coordination between established service providers and expert centers reduce the patient's need to travel to the expert center. Therefore, the patient portal is suitable for use in telerehabilitation. Patients can use the patient portal for individual consultation requests to and from their HCP from home. In this way, HCPs can collect data, monitor patients at home, and consequently change treatment if necessary. As a result, socio-economic costs can be reduced, and patients are thus able to better combine their disease management with their daily social life (20). It is also shown that home-based rehabilitation programs correlate with good patient compliance

(20, 57–59). Existing studies show that MS patients displayed improved socialization after telerehabilitation at home compared to the clinical treatment (20). Consequently, the patient portal is a high-quality eHealth solution for all treatment steps from disease-modifying to symptomatic treatment, and also plays an important role when it comes to telerehabilitation (20, 53).

Perspectives

The implementation of the patient portal highly depends on both technological as well as organizational context factors. First, digital patient portals require a strong integration with medical documentation systems. Proprietary and closed strategies of system providers lead to an insufficient degree of information availability: redundant documentation, interruptions in information flows, and missing transparency of patient status. Therefore, hospitals should move their application systems to support open IT-standards like HL7 FHIR. Secondly, all HCPs need a common understanding of digital patient portals and their management in the inter-sectoral network. This requires a rethinking of their own established processes, behaviors, and cultures. Third, IT-operation of a patient portal is a costly task due to high expectations in security and safety. This needs an adequate refinancing where cost-savings may only appear later in time or indirectly. The reimbursement of costs for the IT operation of the inter-sectoral patient portal must be organized through a multi-stakeholder approach (60).

After successful implementation of the patient portal, the authors see the following perspectives for further development or expansion of the patient portal:

1) **Integration of additional chronic disease patterns:** It is conceivable to also create a patient portal with clinical pathways for Parkinson's disease, diabetes, stroke, or even rare diseases.
2) **Development of a quality manager:** Pathway-based quality indicators can be used to document, monitor, and ideally improve the quality of care for people with MS. They could provide multidimensional quality management tools based on path-based quality indicators for both the patients and the HCPs. For this purpose, the patient portal would be extended by a common path for HCPs and patients. This would make a lasting contribution to patient empowerment, to better integration of care and, above all, to cost reduction through self-management on the part of the patient and quality optimization on the part of the HCP within the framework of recommended MS management (5).
3) **Inclusion of external systems and sensor-based technologies:** As the patient portal allows simple coupling with third-party systems, it is also conceivable to include further external systems, results of remote sensors, wearables, measures of telerehabilitation (e.g., MS Mosaic, Floodlight), and PROs into the patient portal as it is developed (61). Data can be collected continuously at home and not only every three months during a medical consultation (43). Using this approach, more data for the current even more complex management of MS would be available which could be integrated into, as structured for, big data from clinical practices (62).
4) **Development of a privacy manager:** The development of a privacy manager would serve as a tool for patients with chronic illnesses to manage different types of data and data flows within their treatment and to clarify the benefits of these data flows for the patient and to design appropriate security and approval solutions. Through the privacy manager, patients would gain transparency about their own data and its use and can decide for or against the use of their own data for different purposes.
5) **Data Collection using Artificial Intelligence:** Not least, the patient portal is the basis for using artificial intelligence and digital innovations like smart algorithms and expert systems as well as smart communication using the collected well-structured big data from clinical practice. An individualization and constant adaptation of the treatment algorithms by machine learning methods based on data analysis is conceivable. Thus, clinical pathways become adaptable and learn with the patient in the aim of creating personalized pathways. Another idea would be the implementation of chat-bots or avatars, which may help patients access their data in the patient portal.

Limitations

Because the survey was part of a larger requirements engineering process, the paper does not describe the validation (usability tests with patients and HCPs) of the digital portal. This will be reported in the future. Another important issue to consider, when interpreting the survey, is the low response rate of HCPs. In contrast to the patients, HCPs had little interest in completing the questionnaire. This could mean that doctors may have little interest in a patient portal. They might also associate this with an even greater documentation effort. Perhaps they simply did not have time to fill out the questionnaire, or it was too long or too complex for them. But the low response rate can also mean that an (online) questionnaire is not the right instrument for obtaining HCP's opinions concerning a patient portal. This is all the more likely because the HCPs in the workshop were very interested in setting up a patient portal.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation, to any qualified researcher.

ETHICS STATEMENT

Ethical approval and written informed consent was not required according to local legislation and national guidelines.

AUTHOR CONTRIBUTIONS

MB, HS, RK, OM, and TZ conceived the project. MB, IV, RK, OM, and TZ carried out the project. MB, MS, TS, and SF collected data. MB, MS, TS, SF, and IV performed analysis and interpreted results. IV, MB, HS, and TZ wrote the manuscript. All authors reviewed and approved the final manuscript.

FUNDING

This work was supported by the University Hospital Carl Gustav Carus Dresden, the Technical University of Dresden, the MedicalSyn GmbH, and the Carus Consilium GmbH cooperated in the project Integrated Care Portal Multiple Sclerosis. The implementation of the project is made possible by funding from the European Regional Development Fund (ERDF) and the Free State of Saxony. We acknowledged support by the Open Access Publication Funds of the SLUB/TU Dresden.

ACKNOWLEDGMENTS

We would like to thank all patients and HCPs who participated in the project.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2020.00400/full#supplementary-material

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Conflict of Interest: TZ received personal compensation from Biogen, Bayer, Celgene, Novartis, Roche, Sanofi, Teva for the consulting services. TZ received additional financial support for the research activities from Bayer, BAT; Biogen, Novartis, Teva, and Sanofi.

RK received personal compensation from Biogen, Bayer, Celgene, Novartis, Roche, Sanofi, Teva for the consulting services. SF and RK were employed by the company MedicalSyn.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

PERSPECTIVE
published: 12 June 2020
doi: 10.3389/fneur.2020.00464

Can We Improve the Monitoring of People With Multiple Sclerosis Using Simple Tools, Data Sharing, and Patient Engagement?

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Technological innovation is transforming traditional clinical practice, enabling people with multiple sclerosis (pwMS) to contribute health care outcome data remotely between clinic visits. In both relapsing and progressive forms of multiple sclerosis (MS), patients may experience variable disability accrual and symptoms throughout their disease course. The potential impact on the quality of life (QoL) in pwMS and their families and carers is profound. The introduction of treatment targets, such as NEDA (no evidence of disease activity) and NEPAD (no evidence of progression or active disease), that guide clinical decision-making, highlight the importance of utilizing sensitive instruments to measure and track disease activity and progression. However, the gold standard neurological disability tool—expanded disability severity scale (EDSS)—has universally recognized limitations. With strides made in our understanding of MS pathophysiology and DMT responsiveness, maintaining the status quo of measuring disability progression is no longer the recommended option. Outside the clinical trial setting, a comprehensive monitoring system has not been robustly established for pwMS. A 21st-century approach is required to integrate clinical, paraclinical, and patient-reported outcome (PRO) data from electronic health records, local databases, and patient registries. Patient and public involvement (PPI) is critical in the design and implementation of this workflow. To take full advantage of the potential of digital technology in the monitoring and care and QoL of pwMS will require iterative feedback between pwMS, health care professionals (HCPs), scientists, and digital experts.

Keywords: multiple sclerosis, monitoring, 3TEST, patient engagement, technology

OPEN ACCESS

Edited by:
Marcello Moccia,
University of Naples Federico II, Italy

Reviewed by:
Antonio Carotenuto,
University of Naples Federico II, Italy
Nevin John,
University College London,
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Specialty section:
This article was submitted to Neurorehabilitation, a section of the journal Frontiers in Neurology

Received: *15 March 2020*
Accepted: *29 April 2020*
Published: *12 June 2020*

Citation:
Allen-Philbey K, Middleton R, Tuite-Dalton K, Baker E, Stennett A, Albor C and Schmierer K (2020) Can We Improve the Monitoring of People With Multiple Sclerosis Using Simple Tools, Data Sharing, and Patient Engagement? Front. Neurol. 11:464. doi: 10.3389/fneur.2020.00464

INTRODUCTION

Multiple sclerosis (MS) is a chronic inflammatory, demyelinating, and degenerative disease of the central nervous system (CNS). MS affects more than 130,000 people in the UK and over 2.5 million worldwide (1–3). While prediction of the disease trajectory in individual people with MS (pwMS) remains challenging, accrual of chronic disability is the norm (4, 5), particularly if pwMS are left without disease-modifying treatment (DMT) (6). Dependable outcome measures

are highly desirable to assess the clinical course of MS and inform patient management. Given the heterogeneity of clinical presentation, systems involved, and speed of progression, assessing outcomes in pwMS requires systematic, multidimensional tools. Comprehensive follow-up of pwMS has been demonstrated in a number of clinical trials (7–10). However, systematic monitoring of pwMS in clinical practice is often incompatible with the limited time available for patient review (11), particularly when using the expanded disability status scale (EDSS) (12), which nevertheless remains key to determine DMT eligibility (13), and despite its well-rehearsed shortcomings (14).

PwMS with advanced disease, for example those having an EDSS $\geq$ 6.5, and elderly pwMS are at particular risk of being less carefully followed up (15). These patients are more likely not on a licensed DMT and are commonly considered "beyond" immunotherapy, despite mounting evidence that neurologic function can potentially be preserved, even at a later stage of the disease (16, 17).

Here, we provide a perspective on using a new approach of collecting data in pwMS that combines (i) clinical assessments with potential for self-monitoring and (ii) patient-reported outcomes (PROs) using a platform shared between a large data repository, the UK MS Register at Swansea University, and BartsMS in east London, UK. We describe how such point-of-care data collection may serve both research and the individual pwMS in clinic and highlight the role of patient and public involvement (PPI) in facilitating the "buy-in" of pwMS underpinned by some preliminary data on patient engagement with the UK MS Register portal and corresponding data sharing preferences.

QUANTIFYING NEUROLOGIC DISABILITY

The introduction of the EDSS (12) as the key outcome measure of disability in MS DMT trials cemented its role as the neurologist's "gold standard" rating scale of disability in pwMS. However, while clinical trials usually allocate sufficient time to complete and fully document an EDSS (which takes ∼20–30 min), the time constraints of clinical practice regularly lead to either an "estimated" EDSS, or systematic clinical assessments remain patchy, or are not undertaken at all (11). To overcome this shortcoming, various versions of a patient-reported EDSS (PREDSS) have been proposed. These are either paper based, administered via telephone, or, more recently, via an online application, the "webEDSS" (18). Correlation has been observed between EDSS and all versions of PREDSS; however, limitations of agreement were identified, particularly at low EDSS levels (11). However, even if these limitations could be minimized, the non-parametric character of the EDSS, its ambulatory bias, and lack of sensitivity at high values remain problematic. Moreover, decline in cognitive function is not well covered, in spite of its key importance in pwMS, especially given the implications for employment opportunities (19, 20).

As a result, the National MS Society's Clinical Outcomes Assessment Task Force started more than 25 years ago developing a new set of outcome measures. Ultimately, a set of three tests was agreed, making up what was coined the Multiple Sclerosis Functional Composite (MSFC). The MSFC consists of the Paced Auditory Serial Addition Test (PASAT), Timed 25-foot walking (T25ftWT), and the Nine Hole Peg Test (9HPT) and has been implemented in a number of clinical trials (21). However, only this year, 2020, will a DMT licensing trial for the first time use one element of the MSFC, the 9HPT, as its primary outcome measure (22).

"BartsMS" is a clinic–academic partnership based at The Royal London Hospital (Barts Health NHS Trust) and The Blizard Institute/Queen Mary University of London providing clinical care to over 3000 pwMS. Faced with the same discrepancy between high expectations and the reality of limited resources (6), BartsMS introduced a modified version of the MSFC in their clinical practice in 2016. While T25ftWT and 9HPT were retained, PASAT was replaced with the Symbol Digit Modality Test (SDMT; oral version) following the recommendation by Drake and coworkers (23), among others (24). The SDMT has equal psychometric validity to the PASAT and is associated with lesser confounding by training and more congenial for both patient and assessor (23). It takes less time to complete, requires less expertise and experience of the assessor, and, unlike the PASAT, does not require special equipment for auditory presentation of stimuli (24). In practice, we summarize the three elements (T25ftWT, 9HPT, and SDMT) simply as "3TEST." Given a clinical and research focus of BartsMS on advanced MS, i.e., people with an EDSS of $\geq$ 6.5 (25), the ABILHAND questionnaire is also regularly administered to capture perceived manual ability (26). Obtaining such "real world" outcome measures in routine clinical practice and trials has also been recognized by the European Medicines Agency (EMA) as an important component of disease management (27).

THE EVOLVING ROLE OF REMOTE SELF-MONITORING

The relative simplicity of the MSFC or variations thereof, such as the 3TEST, combined with advances in technology and ever-increasing online resources and capabilities have led to the expansion and uptake of self-monitoring applications (28). Self-monitoring enables tracking the disease course in pwMS unable to travel to clinic, e.g., due to their disability or them living in remote locations. Given the often-extended intervals between follow-up in clinic (commonly 6–12 months), systematic self-monitoring may improve detection of changes not captured during visits, including relapses and disability accrual, thereby enabling earlier detection of disease progression and trajectories of long-term outcomes. Moreover, self-monitoring has inherent potential to empower pwMS to manage their condition pro-actively, with likely benefits for their care and self-management (29). Alongside other measures, such as written decision aids (30), self-monitoring may help remove hierarchical barriers and level the platform for shared decision-making between health care professionals (HCPs) and pwMS. It would be expected that such change will improve treatment satisfaction and adherence (31). Against this backdrop, numerous self-assessment tools

FIGURE 1 | The hub/spoke system between BartsMS and the UK MS Register. **(A)** The interaction between the BartsMS service & Database, and the UK MS Register. **(B)** My MS Hub page on the patient portal. **(C)** Graph of Multiple Sclerosis Impact Scale (MSIS29 V2) results viewed in the patient portal. Accompanying description for people with MS: "Used to measure the impact that your MS is having on you physically and psychologically at any given time. This questionnaire was designed specifically for MS. It means that researchers can measure how much your MS affects your quality of life. It is increasingly being used in MS research and clinical settings. What the graph means: the MSIS is composed of three scores, a total, a psychological sub-score and a physical sub-score. In this graph we show the psychological and physical sub-scores. In both Scales, higher values indicate that your MS is causing you more trouble and lower ones indicate less impact." **(D)** Graph of EQ-5D 3L results viewed in the patient portal. Accompanying description for people with MS: "This is one of the most commonly used health status measurements. It is not MS specific and so it can be used to make comparisons with various other health conditions/chronic diseases. What the graph means: the EQ5D has five questions specifically related to aspects of your general health and one scale marked out of 100 in which you indicate your overall quality of life. High scores indicate a better overall quality of life".

have been developed (32, 33). As part of this effort, our group developed portable versions of the 9HPTs and the T25ftWTs (34, 35), while the UKMSR produced an online version of the SDMT (MSiDMT) (36).

In addition, wearable technologies, including motion detecting devices (MTDs) and smartphone applications may facilitate minimally intrusive assessment of outcomes such as step count, walking speed, and gait (37) and support neurorehabilitation (38).

A MODEL OF INTEGRATED MONITORING AND PATIENT ENGAGEMENT

Results from tests that (i) are relatively straightforward to implement in clinic and (ii) can be translated into self-monitoring tools can be combined with PRO questionnaires and fed into the patient record, which, in health care settings covering large numbers of pwMS, is usually an electronic health record (EHR). EHRs facilitate the timely recording of patient data and the simultaneous navigation by multiple HCPs from different specialities (39). Coding terminology, such as Systematized Nomenclature for Medicine (SNOMED), provides a powerful resource to collate individual patient data as well as to identify, stratify, and audit patient cohorts and outcomes.

We use the generic Barts Health NHS Trust-wide EHR Cerner Millennium Clinical Record System (CRS). This system enables extraction of coded information to populate our database of pwMS (the "BartsMS Database") in Excel (40), thereby providing both an individual record and a point-of-care data collection, including 3TEST data, fed by the various HCPs at the Trust involved in the care of the pwMS. Our dataset is further enriched by the UK MS Register (UKMSR), an MS Society (UK)-sponsored resource that collects PRO data on pwMS throughout the UK (41). The UKMSR was conceived on the understanding that PRO data are important to capture the experience of pwMS and their families, friends, and carers (42–44). PROs are also commonly used as secondary endpoints in clinical trials to determine and compare the effect of DMTs. The core validated instruments collected by

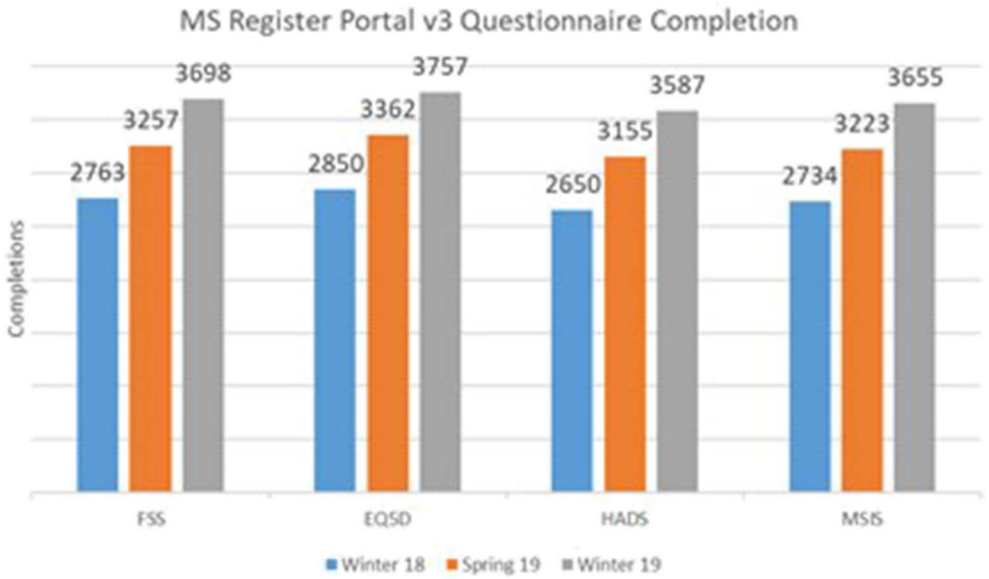

FIGURE 2 | Core Questionnaire Response rates following PPI and redesign of the UK MS Register portal.

the UKMSR are EuroQol 5D (EQ-5D), Multiple Sclerosis Impact Scale 29v2 (MSIS-29), Hospital Anxiety and Depression (HADS) Scale, Fatigue Severity Scale (FSS), the Multiple Sclerosis Walking Scale (MSWS-12), and Patient Determined Disease Steps (PDDS) (45–51). The webEDSS is also available as an *ad hoc* questionnaire (52).

Since 2017, BartsMS and the UKMSR have been developing a hub/spoke monitoring system (**Figure 1**). The intention of the algorithm is to (i) facilitate research through high-quality data collection, (ii) support the clinical service provision with PRO data, and (iii) enable the latter via a patient portal. PwMS who consent to join the UKMSR will have their minimum dataset (demographics, MS history, risk factors, disease course, EDSS scores, relapses, DMT, and symptomatic information) collected and securely uploaded via a REDCap electronic clinical record form (53). In addition, pwMS are prompted via email, at regular (currently 6-monthly) intervals, to fill in PRO questionnaires. This information can then be linked to their unique study ID provided at the hospital site, and thereby merged with their clinical record.

PATIENT ENGAGEMENT

We learned that patient and public involvement (PPI) is pivotal to maintain and expand data collection through the UKMSR. Valuable insights and feedback were provided through a PPI meeting held at The Royal London Hospital (Barts Health NHS Trust) on 16 February 2018. Key outcomes of this engagement day were (i) a re-designed, visually more attractive website enabling easier navigation and providing better sectioning, including a "My MS" hub page. This hub contains easily identifiable and accessible open questionnaires, including estimates of the time required for completion. This feature also provides pwMS with a snapshot of the information they have contributed and highlights any data that they should still provide; (ii) radio boxes for questionnaires, rather than drop-down menus since less mouse movement is required, making it easier to navigate for pwMS with upper limb function impairment; (iii) reduced frequency of questionnaire responses requested (bi-annually instead of quarterly); (iv) more tangible benefits for UKMSR subscribers, who were keen to receive comprehensive feedback about their collected questionnaire data—we therefore decided that the facility of viewing personal response data should be provided as an option; (v) since September 2018, participants who join the UKMSR and opt in to feedback are being offered a downloadable version of their results. By December 2019, 67% of new subscribers (total n = 2712) had had opted into this facility. This is designed so that it can be taken along to clinic appointments. Information is displayed in easily accessible graphs, allowing pwMS to track their condition over time. Explanations in lay terms are included about what the instruments and graphs mean and their relevance to pwMS (**Figures 1C,D**).

Further insights from our PPI exercise included an understanding that pwMS wanted the UKMSR portal to enable them (i) to have better control over their health care including treatment options, (ii) access to clinical trials, and (iii) improved self-management. PwMS were also passionate about furthering research both for short-term benefit and for future generations, including their own children.

To estimate the effect of our response to the PPI input received on the rate of questionnaires, we extracted the number of completed questionnaires at three time points; Winter 2018 (before implementation of the above changes to the portal),

Spring 2019, and Winter 2019. Data were extracted from the UKMSR production databases running Microsoft SQL Server 2014.

Figure 2 illustrates a significant increase in the number of completed questionnaires between the launch of the new website in Winter 2018 and the latest cutoff in Winter 2019. This increase suggests a significant impact of PPI on the new UKMSR portal design and functionality.

DISCUSSION

Optimizing the landscape of individualized, effective, and compassionate care with and for pwMS remains a work in progress. Whereas clinical trials provide data on a cohort level, the evidence produced can only provide a backdrop for decisions that need to be tailored to the individual pwMS. Clinical monitoring is essential to detect treatment success and failure, in order to make individual decisions. While various digital tools for disease monitoring in pwMS have been developed, their value in clinical practice is not yet established, and their adoption limited (54). We found validated measures that are easily applicable and straightforward to interpret a useful way to quantify change in an era where pwMS expect their care to catch up with the efficacy of the latest DMTs. The administration of 3TEST does not require any special qualification—virtually any HCP can be trained to apply it in a short timeframe. Since all three parts of the 3TEST can be done remotely, the limit for self-monitoring is now mainly a question of frequency and logistics (how often to test, how to feedback results to the health care team, and how to embed the data in the daily routine of neurologists and MS specialists between appointments). The simplicity and compatibility for remote testing of 3TEST also highlight the potential for relatively straightforward multi-center adoption and inclusion in large datasets, such as the UKMSR or MSBase (55), and there is obvious potential for remote testing in exceptional situations, such as a pandemic (56). Furthermore, 3TEST is likely going to be of use when screening for trials where measures other than the EDSS are being used for inclusion as well as outcome (22). New systems intended to both serve individual monitoring of pwMS and contribute to large datasets, such as Floodlight (33, 57), will need to be validated using well-established tests such as those combined in 3TEST (32).

Our experience trying to combine clinical and PRO data collection via the UKMSR in order to facilitate databasing for research, service audit, and individual patient care highlights the important role of PPI throughout the design and implementation process. To truly deliver patient-centered care and at the same time enable high-quality data collection, any system for pwMS needs to be developed jointly with pwMS. In our example, PPI led to a significantly increased number of completed PRO questionnaires. We are currently optimizing and streamlining mutual data exchange between BartsMS and the UKMSR to provide an integrate model of point-of- care data collection. This system may provide a model of data collection and sharing that can be adopted by other centers across the UK and beyond.

DATA AVAILABILITY STATEMENT

All datasets generated for this study are included in the article/supplementary material.

AUTHOR CONTRIBUTIONS

KS initiated the BartsMS Database and conceptualized the setup between the UK MS Register and BartsMS clinical interface, which the team helped establish. KA-P, RM, and KS drafted the manuscript. CA, AS, and KT-D contributed toward the subsequent revisions. RM and EB performed the data extraction and analysis. All authors read and approved the final manuscript.

FUNDING

KA-P was supported by the National Institute for Health Research North Thames Clinical Research Network. The UKMSR was funded by the Multiple Sclerosis Society of Great Britain & Northern Ireland. The initiation and early maintenance of the BartsMS Database were supported by non-promotional research grants from Novartis Pharmaceuticals UK Ltd.

ACKNOWLEDGMENTS

We would like to thank members of the BartsMS advisory group led by Alison Thomson for their valuable contributions toward development of the UK MS Register portal and collaboration with the BartsMS clinical service.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The handling editor declared a past co-authorship with one of the authors KS.

frontiers in Neurology

ORIGINAL RESEARCH
published: 16 June 2020
doi: 10.3389/fneur.2020.00583

The Use of Social Media and Digital Devices Among Italian Neurologists

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Edited by:
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The University of Queensland, Australia

Reviewed by:
Hyungsoon Im,
Harvard Medical School, United States
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Specialty section:
This article was submitted to Neurorehabilitation, a section of the journal Frontiers in Neurology

Received: 06 July 2019
Accepted: 20 May 2020
Published: 16 June 2020

Citation:
Lavorgna L, Brigo F, Abbadessa G, Bucello S, Clerico M, Cocco E, Iodice R, Lanzillo R, Leocani L, Lerario A, Moccia M, Padovani A, Prosperini L, Repice A, Stromillo M, Trojsi F, Mancardi G, Tedeschi G and Bonavita S (2020) The Use of Social Media and Digital Devices Among Italian Neurologists. Front. Neurol. 11:583. doi: 10.3389/fneur.2020.00583

Background: Digital devices and online social networks are changing clinical practice. In this study, we explored attitudes, awareness, opinions, and experiences of neurologists toward social media and digital devices.

Methods: Each member of the Italian Society of Neurology (SIN) participated in an online survey (January to May 2018) to collect information on their attitude toward digital health.

Results: Four hundred and five neurologists participated in the study. At work, 95% of responders use the personal computer, 87% the smartphone, and 43.5% the tablet. These devices are used to obtain health information (91%), maintain contact with colleagues (71%), provide clinical information (59%), and receive updates (67%). Most participants (56%) use social media to communicate with patients, although 65% are against a friendship with them on social media. Most participants interact with patients on social media outside working hours (65.2%) and think that social media have improved (38.0%) or greatly improved (25.4%) the relationship with patients. Most responders (66.7%) have no wearable devices available in clinical practice.

Conclusion: Italian neurologists have different practices and views regarding the doctor–patient relationship in social media. The availability of digital devices in daily practice is limited. The use of social networks and digital devices will increasingly permeate into everyday life, bringing a new dimension to health care. The danger is that

advancement will not go hand in hand with a legal and cultural adaptation, thus creating ambiguity and risks for clinicians and patients. Neurologists will need to be able to face the opportunities and challenges of this new scenario.

Keywords: digital health, social media, digital devices, app, wearable devices

INTRODUCTION

The use of digital devices and the introduction of online social networks have transformed many aspects of clinical practice. Both patients and physicians are increasingly using the Internet and social media platforms to obtain, provide, share, and comment on health information (1, 2). On social media, users can create and share content and can take part in social networking collaborative projects (e.g., Wikipedia), content communities (e.g., YouTube), social networks (e.g., Facebook), web logs (blogs), or virtual games (3, 4). Each of these activities can be used by physicians or by patients to communicate, retrieve, or convey information on health issues or diseases, with an increasing accessibility and widening access, compared to conventional media (5).

An ever-growing number of physicians use social media to share health-related information on a range of conditions, to enhance professional development, but also to facilitate or reinforce doctor–patient relationship, sometimes even providing online consultations (4). This led to some ethical and legal issues, mainly related to the maintenance of boundaries or to the respect of privacy and personal data (6). Finally, digital devices, including wearable devices and exergames (i.e., the use of commercial video games for retraining impaired functions), are increasingly entering the clinical practice, complementing the more traditional tools for monitoring performance or providing exercise (2, 7–11).

So far, few studies have explored attitudes, awareness, opinions, and experiences of neurologists toward social media and digital devices. Thus, we have investigated this in a sample of Italian neurologists.

METHODS

This cross-sectional study was conceived by the study group on "Digital Technology, Web and Social Media" of the SIN (Italian Society of Neurology). Between January and May 2018, each member of the SIN received an e-mail invitation to take part in a written survey aiming to collect information on the attitude of Italian neurologists toward social media and digital devices in the clinical setting. Procedures for obtaining informed consent and protecting participants were approved and monitored by the study group of the SIN coordinating the survey. After having flagged the consent to proceed anonymously (GDPR EU2016/679), the involved neurologist had to fill in a structured survey. A preliminary version of the survey was derived from (4) and circulated among a number of coauthors of this manuscript for internal revision before submission to all participants. The survey mainly consisted of questions aimed at collecting demographic data of responders (age, geographical region), type of digital devices (including wearable devices) available or used in clinical practice and reasons for use, attitude toward social media in communication with patients, and apps used for medical purposes.

Frequencies and percentages were used for the presentation of categorical variables and responses. Three univariable logistic analyses were performed to evaluate the impact of age, sex, and geographical area (recorded in three classes: North, Center, South, and Islands) on the use of social media to communicate with patients. Variables with association with the outcome ($p < 0.01$) at the univariable level were then included in a multivariable model. All analyses were performed with Stata 14.1 and $p < 0.05$ (two-sided) were considered statistically significant. The study was approved by the Ethical Committee of the University of Campania "Luigi Vanvitelli."

RESULTS

A total of 2,434 invitations were sent by e-mails to all members of the SIN. At deadline (May 31), 405 (16.6%) neurologists took part in the study. This sample size gives a margin of alpha error <0.05 considering a confidence level of 95%.

Most participants were aged between 30 and 49 years (50%), 51% (206 out of 405) females and 49% (199 out of 405) males; 31% of the responders were from South Italy, 25% from North-West and 16% from Nord East Italian regions, 18% from Central Italy, and 9% from Italian islands. Most neurologists reported that they were available to their patients irrespective of visiting hours.

At work, 95% of responders use the computer, 87% the smartphone, and 43.5% the tablet. These devices are used to obtain health information (91%), to maintain contact within the medical community (71%), to provide information to colleagues and patients (59%), and to receive clinical updates (67%). Most participants (56%) use social media to communicate with patients, whereas 65% are not in favor of a friendship with patients on social media. The most frequently used social medium at work is WhatsApp (82.5%), followed by Skype (43.6%), Facebook (31.9%), and LinkedIn (29.1%). Similarly, at home, the most used social media are WhatsApp (94.8%), followed by Facebook (65.7%), and Skype (48.9%). Most participants interact with patients on social media outside working hours (65.2%) and think that social media have improved (38.0%) or greatly improved (25.4%) the relationship with patients. Apart from social media, 35% of responders have a personal webpage. In the multivariate analysis, age groups 40–49, 50–59, and 60–69 years and originating from Center and South Italy were associated with higher use of social media

to communicate with patients compared, respectively, with age between 20 and 29 years and originating from the North area.

The vast majority of participants (95%) report to have visited patients who had already made a self-diagnosis on the Internet; 70.6% warn their patients against websites providing unreliable or imprecise information, whereas 55.3% advise reliable online sources of information, trying to gain the trust of patients by keeping up to date on health-related news circulating on the Web, demonstrating their unreliability relying on results of scientific studies. Most responders (66.7%) report that they have no wearable devices (i.e., iGloves, eye-trackers, skin patches, or fit watches) available in their clinical practice. The use of consoles like Xbox, Wii, or PlayStation for physical exercise are suggested by 60% of respondents (243 out of 405).

Detailed results and the survey (English version) are provided as **Supplementary Material**.

DISCUSSION

To the best of our knowledge, no study has explored how neurologists use social media and digital devices to interact with patients and provide information on diseases yet, though some previous studies assessed the use of social media or digital devices by health care professionals (7).

The most frequent reasons for using social media were to obtain health information, maintain contact within the medical community, provide information to colleagues and patients, and receive clinical updates. These findings emphasize the wide range of opportunities provided to physicians by social media and are consistent with the results of a systematic review that identified the following seven main uses of social media platforms for health communication: (1) providing health information on a range of conditions; (2) providing answers to medical questions; (3) facilitating dialogue between patients to patients, and patients and health professionals; (4) collecting data on patient experiences and opinions; (5) use for health intervention, health promotion, and health education; (6) reducing stigma; and (7) providing online consultations (4).

In our study, about half of the responders (56.3%) reported using social media to communicate with patients; however, 65% of the neurologists were against accepting a friendship with patients on social media. This finding confirms that, despite most participants reporting that social media have improved or greatly improved the relationship with patients, the neurologists' general behavior is aimed at maintaining boundaries in an online doctor–patient relationship. Conversely, the favorable opinion toward friendship with patients expressed by one third of participants raises potential privacy and ethical issues in clinical practice. More specifically, Italian rules on medical confidentiality (Codice di Deontologia Medica, FEDERAZIONE NAZIONALE DEGLI ORDINI DEI MEDICI CHIRURGHI E DEGLI ODONTOIATRI, 2014, updated 2016; available online at: https://www.omceo-to.it/00666/DOCS/8_y-codice-deontologia-medica-2014.pdf) still do not explicitly include or report any specific guidance on securing and sharing patient information on social media or, more generally, on personal online communication.

Online relationship between physicians and patients is indeed viewed by doctors as ethically problematic. Here, the major issues that can arise in online interactions involve the difficulties in setting boundaries or in developing empathy in the doctor–patient relationship due to the lack of physical contact, as well as the therapeutic interaction. These ethics issues are likely to be even more relevant in relationships occurring in social media or social networks. However, the use of social media can prove useful and beneficial to patients through providing and sharing health-related information; it may strengthen professional connections and advance understanding of which individual factors can influence public health (6).

A study conducted among US medical students and physicians showed that most responders considered it not ethically acceptable to interact with patients using online social media and networks, for either social (68.3%) or patient-care (68.0%) reasons (12). Interestingly, 48.7% of responders did not believe that social media could improve patient–doctor communication, also because of problems related to protection of patient confidentiality (79%). However, this study was conducted almost 10 years ago, and the attitude has possibly changed in more recent years. More recently, a survey conducted on 187 Australian doctors showed reluctance to engage with the social media despite the fact that they represent a common feature of clinical practice (13). Although most of them used social media privately, only about 20% had received a "friend request" from a patient. Open issues remained and were specifically related to protection of personal information online and to legal issues (13).

The role of social media to convey health-related information has been evaluated in a few studies. A small survey conducted in 17 physicians emphasized challenges and difficulties arising with this type of communication, including "uncertainty about boundaries or strategies for social media use," lack of interaction, and the feeling that time spent on social media could be an obstacle to patient care (14).

Our study shows that higher use of social media to communicate with patients was associated with older age and origin from Center and South Italy. This might be explained by the fact that physicians aged between 20 and 29 years, hence just graduated or still residents, do not usually have a deeper relationship with their patients; furthermore, physicians in Northern Italy could be more detached with their patients and less prone to use social media to communicate with them. Interestingly, in our study, almost the total of responders (95%) reported to have visited patients who had already made a self-diagnosis on the Internet, underlying the increasing role of the Internet as a source of medical information by the general population. Most responders tried to develop or enhance a critical attitude of their patients toward information retrieved online, by warning patients against websites providing unreliable or imprecise information, or by even advising reliable online sources of information. This has relevant public health implications, suggesting that instead of discouraging the use of the Internet, physicians should educate patients to a more critical use of it. Furthermore, they could also take advantage of the increasing use of the Internet as a source of information, for instance by gaining the trust of patients by keeping up to date

on health-related news circulating on the Web or demonstrating their unreliability by referring to results of scientific studies.

Our survey also assessed the use and/or prescription of wearable devices including exergames in daily practice. Most responders (66.7%) reported that they had no wearable devices (i.e., iGloves, eye-trackers, skin patches, or fit watches) available in their clinical practice. Although we did not address this specific issue, it is likely that wearable devices are more accessible and easy to obtain in the research setting compared to the clinical one. Although they are increasingly used in clinical practice, mainly for rehabilitative purposes, so far, no study has investigated the physicians' attitude toward them (2). However, a survey conducted in physiotherapists and elderly subjects showed that the former are aware of the functions and possible applications of exergames, but they do not think that they will have a relevant influence on traditional rehabilitation tools. Conversely, older people have no interest or even information on their function but could be willing to try them for rehabilitation purposes (15).

There have been great efforts to develop electronic health records providing patients with access to their clinical data. Still, access rights are variable across countries and, so far, this possibility has never been fully explored in Italy (16). However, we cannot exclude that, in the future, electronic health records with patient access and more interactive environment could act as a social platform for customized medical information.

A limitation of this study is the conduction in Italy, a country with the lowest use of the Internet for health information seeking in the European Union (17), and easy-to-access social networks could have compensated this difference that, however, would be expected to reduce over time.

Comparing our data to the surveys available in the literature and previously conducted among physicians, we were not able to identify features indicative of a specific attitude or expectation of neurologists toward social media and digital devices. Italian neurologists have different practices and views regarding the doctor–patient relationship in online social media. The availability of digital devices in daily practice is extremely limited.

Soon, the ever-growing use of online social networks and availability of digital devices will increasingly permeate into everyday life, bringing a new dimension to health care. Benefits will include the increased availability to generate, share, and comment on health issues, with the ultimate aim of improving health outcomes and communication practices. However, this also carries risks associated with spreading unreliable or low-quality information and protection of informational privacy. Rules on medical confidentiality should formally address the issue of securing and sharing online patient information as well as the relationship with patients on social media. The greatest danger is that technological advancement will not go hand in hand with a legal and cultural adaptation, thus creating ambiguity and risks for clinicians and patients. Neurologists and health care personnel will need to be able to face the opportunities and challenges of this new scenario.

DATA AVAILABILITY STATEMENT

All datasets generated for this study are included in the article/**Supplementary Material**.

AUTHOR CONTRIBUTIONS

All co-authors have made a substantial contribution to the design, data collection, analysis of the research, drafting of the manuscript, and have reviewed and accepted the contents of the manuscript prior to its submission.

ACKNOWLEDGMENTS

Simone Eboli Digital Humanist, for the digital support.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2020.00583/full#supplementary-material

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Reviewer KS declared a past co-authorship with one of the authors, LLa, to the handling editor.

frontiers in Neurology

PERSPECTIVE
published: 16 June 2020
doi: 10.3389/fneur.2020.00445

Data Collection in Multiple Sclerosis: The MSDS Approach

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Multiple sclerosis (MS) is a frequent chronic inflammatory disease of the central nervous system that affects patients over decades. As the monitoring and treatment of MS become more personalized and complex, the individual assessment and collection of different parameters ranging from clinical assessments via laboratory and imaging data to patient-reported data become increasingly important for innovative patient management in MS. These aspects predestine electronic data processing for use in MS documentation. Such technologies enable the rapid exchange of health information between patients, practitioners, and caregivers, regardless of time and location. In this perspective paper, we present our digital strategy from Dresden, where we are developing the Multiple Sclerosis Documentation System (MSDS) into an eHealth platform that can be used for multiple purposes. Various use cases are presented that implement this software platform and offer an important perspective for the innovative digital patient management in the future. A holistic patient management of the MS, electronically supported by clinical pathways, will have an important impact on other areas of patient care, such as neurorehabilitation.

Keywords: multiple sclerosis, documentation, digital patient management, post-authorization safety study, MSDS[3D]

OPEN ACCESS

Edited by:
Marcello Moccia,
University of Naples Federico II, Italy

Reviewed by:
Viktor Von Wyl,
University of Zurich, Switzerland
Peter Kosa,
National Institutes of Health (NIH),
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Specialty section:
This article was submitted to Neurorehabilitation, a section of the journal Frontiers in Neurology

Received: *15 December 2019*
Accepted: *27 April 2020*
Published: *16 June 2020*

Citation:
Ziemssen T, Kern R, Voigt I and Haase R (2020) Data Collection in Multiple Sclerosis: The MSDS Approach. Front. Neurol. 11:445. doi: 10.3389/fneur.2020.00445

INTRODUCTION

The low average age at diagnosis and an only slightly reduced life expectancy make multiple sclerosis (MS) a long-term disease that is relevant to patients for decades (1, 2). At the same time, the high inter- and intra-individual variability in the course of the disease constantly leads to new treatment situations (3). As a result, numerous disease data with information about complaints, symptoms, as well as diagnostic and therapeutic measures accumulate within the framework of medical and therapeutic care (4).

Today, certain therapeutic options are linked to the presence of certain disease characteristics (5). When prescribing specific therapies, the effectiveness must be documented individually for each patient. The differentiation between responders and non-responders of immunomodulatory therapies is not conceivable without efficient specific documentation (6, 7). When the documentation of psychological symptoms and other medical disciplines are added, the necessity for a complex course documentation becomes clear (8, 9). In addition, a large number of healthcare institutions depend on a timely and holistic exchange of information between the partners involved (10, 11).

Patient Documentation

Electronic patient data management represents a suitable implementation for the MS progress documentation of all the points mentioned. Linkable database systems allow individual courses

to be displayed in a standardized way over many years, and the data generated can be stored in a readable, transparent, and quickly retrievable form (12, 13). Automated calculations lower the threshold for the systematic application of established scales such as Expanded Disability Status Scale (EDSS) or Multiple Sclerosis Functional Composite (MSFC), which are indispensable for the quantification of neurological deficits (14–19). In addition to the standard instruments, patient-reported outcomes (PROs) increasingly complete the holistic assessment of the disease course (20, 21). The regular use of scales is now a prerequisite in expert recommendations regarding MS therapy. Patient-specific documentation and management is becoming more and more important in the growing field of neurorehabilitation in MS (22). Of particular importance is how complex and individualized neurorehabilitation is designed. Common approaches to neurorehabilitation include the treatment of individual symptomatic impairments, often using motor training approaches (23, 24). Because of the wide range of symptoms and disabilities in MS, single symptomatic interventions can only be seen as part of the rehabilitation program. Comprehensive information and education of patients and relatives and other social and environmental factors are equally important (25). The more stakeholders are involved and the more information is collected and processed, the more complex and costly the processes of neurorehabilitation become, which leads to the necessity of a measurable efficiency of rehabilitation.

Due to the large amount of data to be processed, the large number of communicating persons, and the demands of the healthcare system, all these points predestine electronic data processing for use in the holistic documentation and management of progression in MS (26–28).

eHealth for Documentation of Patient Data

The coordinated exchange of health-related information is associated with numerous promising opportunities for daily care in clinics and practices supporting decision-making and the treatment process as a whole (10, 29). Technologies such as an electronic medical record (EMR) enable the rapid exchange of health information between patients, practitioners, and caregivers, regardless of time and location, with the EMR mainly exchanging data between health professionals in single entities of the health system (4, 22, 30–33). Today, every part of the treatment process—from diagnosis, treatment selection, and application to patient education and long-term care, including drug treatment and rehabilitation—can be complemented by a quality-assured implementation of information technologies in healthcare ("eHealth"), which also takes into account data security standards and concerns (4, 34, 35).

Such eHealth services are generally considered useful for physicians and nurses in neurological practices to improve clinical documentation, data collection, and diagnosis of specific MS symptoms, doctor–patient communication, and patient education (33). Practices specialized in MS have an increased need for eHealth services to document interventional and non-interventional drug treatment and rehabilitation studies (36).

Despite the many arguments for detailed electronic documentation of people with MS (pwMS), implementation in clinical practice is difficult and has not yet been standardized. The most significant reason for the lack of acceptance and active use of electronic documentation services is the additional time required. Due to the problematic reimbursement situation for physicians, the additional time for detailed documentation is often lacking, especially since there are no comprehensive initiatives by the funding agencies for this problem, which can be aggravated by non-synergetic double documentation tasks resulting from incompatible data platforms. The interoperability of health data between hospital information systems, documentation systems of physician networks or cooperation projects, study-related platforms, and register databases is often severely limited. Various electronic documentation systems developed by the pharmaceutical industry were not followed up after more or less lengthy pilot phases. Overall, it became apparent how problematic a documentation platform dependent on a single pharmaceutical manufacturer can be.

Cross-project documentation systems or systems that are not limited to a single purpose increase the value and service life of health data. Recent advances in the diagnosis and treatment of MS require far-reaching policy changes in clinical reality in order to develop a holistic and efficient approach to MS management (37). In an ideal scenario of well-connected healthcare providers, the EMR serves as a central source of health information by aggregating multi-modular information from different domains and making it accessible according to the needs of all users, not only in-house healthcare professionals. Due to the heterogeneity of MS, it is of great importance to establish reliable and valid measuring instruments to capture disease-relevant characteristics from the patient's point of view in addition to clinical and imaging procedures (3).

Integration of the Patient's Perspective

Factors reported by patients themselves such as symptoms, health status, health-related quality of life, but also adherence to and satisfaction with treatment, as well as treatment outcomes, are increasingly becoming the focus of attention. PROs are collected using standardized questionnaires and provide valuable information on the effectiveness of interventions and therapies (20, 38–41). The patients' symptoms and physical impairments remain unexplored by the healthcare providers, especially in the intervals between clinic visits (42–45). In addition, pwMS are often affected by varying degrees of cognitive impairment and may forget what they felt a week or two before planned visits (46–48). One possible solution to this problem is for patients to answer questions about their symptoms electronically, either via Internet or through their app-based electronic devices such as smartphones or tablets (49–51). As we have analyzed, patients are happy to use digital instruments to document their disease status (11, 52). Their responses could then be transferred to the health record and various doctors could receive automated notifications of alarming symptoms, which enables the step from data collection to electronically assisted disease management.

Unlike paper-based documentation with its limitations (missing, ambiguous, or contradictory data), electronic documentation with tablets or smartphones can eliminate these problems (11, 51, 53, 54). This enables a faster and more efficient collection of information, offers high security in data storage, and is environmentally friendly.

In order to enable documentation across cases and institutions, all findings, diagnoses, treatment measures, and reports in the future will be stored in an EMR that must also be accessible and usable by the patient. Such a patient record is the starting point for a digitally supported patient management. It enables the physician to quickly gain an overview of all important data as well as the course of the disease and to offer a personalized treatment to the patient in a process of shared decision-making based on shared information. For example, prescribed medication can be read or a comprehensive clinical picture can be created. The issuing of electronic prescriptions, referrals, or doctor's letters can also contribute to more efficient and cost-effective healthcare. Medical care that is specially tailored to the patient improves the course of the disease by reducing side effects to a minimum. In addition, the acceptance of the medication is increased, which in turn improves the effect of the medication (55–58).

THE MSDS APPROACH

From MSDS Clinic to MSDS[3D]

The Multiple Sclerosis Documentation System (MSDS) with its clinical focus was developed in Dresden, Germany. It has established itself as an input platform and is constantly being further developed as a desktop version and for web browsers (24, 59, 60). The first MSDS version (*MSDS Clinic*) was specially designed for MS outpatient departments at universities in 1999 for the structured collection of clinical data on the pathology of MS as well as for the writing of letters to physicians. For the first time, it allowed several users to access the database at the same time. MSDS found a growing number of users in Germany and was used in the MS Registry pilot project. In its early EMR-like version, MSDS allowed the user to enter patient data, clinical history and clinical examination data as well as results and treatment details. For the first time, it was possible to graphically display the course of an individual patient and create medical reports (60).

MSDS Practice is a modified version of the above mentioned clinical MSDS version designed specifically for neurological outpatient practices. In contrast to *MSDS Clinic*, *MSDS Practice* addresses the special requirements of neurological practices through a reduced scope of documentation and a simplified user interface, and it combines a transparent presentation of the course of disease with diagnostic and therapeutic decisions in everyday practice (59).

In view of the increasingly complex therapies, the eHealth project group at Dresden University Hospital developed the multidimensional patient management system *MSDS*^{3D} in cooperation with MedicalSyn GmbH in 2014. As a further development of the *MSDS Clinic*, *MSDS*^{3D} is designed to support physicians in performing more complex processes (e.g., treatment management) and integrates patient, nurse, and physician into these processes. Especially in the case of complex long-term diseases such as MS, those involved in the treatment process want a special, intelligent management system that goes beyond pure documentation (61). In addition, the system can be used not only to enter and interpret patient data, but also as an interactive system to provide information to the patient. Interaction with patients takes place either via multi-touch systems as an interactive patient terminal or via mobile devices such as the patient's smartphone. With the development of *MSDS*^{3D}, the step from pure patient documentation to an adaptive patient management system for MS was thus completed (4, 24).

Patient Data in MSDS[3D]

MSDS^{3D} can be used to conduct the preliminary and accompanying examinations necessary for the application of complex therapies within a defined clinical pathway, as well as patient surveys on various aspects of their disease. The integrated survey system for questionnaire-based data collection is equipped with a user interface specifically designed for pwMS. Currently, the Early Mobility Impairment Questionnaire (EMIQ) (62), the Multiple Sclerosis Walking Scale (MSWS-12), and Multiple Sclerosis Health Resource Survey (MS-HRS) (63, 64) are integrated in the questionnaire module. The medical staff manages the survey process (e.g., starting the survey) and provides assistance in answering questions. The mobile terminals are controlled by the *MSDS*^{3D} system located locally in the treatment center via a special server, which also regulates the data flow to and from the patient. Anonymity and data protection are guaranteed in a complex procedure with encrypted transmission. Patient surveys can thus be carried out digitally, as well as cognitive testing (Paced Auditory Serial Addition Test, Symbol Digit Modalities Test) and gait analysis (Timed 25-Foot Walk, 2 Min Walk Test), which have also been integrated into the system (65, 66).

Connecting MSDS[3D] to Other Data Infrastructures

The *MSDS*^{3D} infrastructure is also used for the European cohort of the Multiple Sclerosis Partners Advancing Technology and Health Solutions (MSPATHS) (67). This Biogen-funded global program for MS centers in Europe and North America successfully integrates digitally collected PROs into routine clinical care. Data collected via tablet includes general information about the person, health insurance, medical history of MS, use of medication and stimulants, laboratory results, vital signs, and MRI results. With the Multiple Sclerosis Performance Test (MSPT) (17, 18) in addition to the anamnestic parameters, all components of the MSFC as well as Neuro-QoL domains are recorded in a standardized manner, which can be visualized back to physician and patient using *MSDS*^{3D} (17, 18).

Various specific *MSDS*^{3D} modules allow standardized documentation and visualization of visit schedules and obligatory examinations using a vertical timeline that represents the examination times and horizontally arranged tasks with detailed parameters to be recorded. Administrative

functions (e.g., creating a patient, registering a patient for an examination) and evaluation mechanisms are integrated into the patient management system via a toolbar. In diagnostic–therapeutic terms, the implemented instruments are based on the guidelines of the respective professional associations.

Further developments of *MSDS*^{3D} enable the web-based system-independent use of the platform and the integration of further participants in the treatment process. In addition, image and laboratory data relevant to MS can be captured in the *MSDS*^{3D} platform so that for the first time they can be systematically investigated combined with clinical data. By implementing lab data into the *MSDS*^{3D} transferred from the lab server, the analysis of laboratory data from the real world could be performed, easily linking clinical and laboratory data (68, 69).

MSDS^{3D} as a Platform for Post-authorization Safety Studies

Particular emphasis was placed on the systematic collection of post-marketing safety data, as randomized controlled trials are not able to identify rare adverse events (70). This was recently shown in a systematic analysis of real-world studies for Fingolimod as an example (71). These post-authorization safety studies (PASS) are used to collect real-world data reflecting the real-life safety profile and utility of drugs, which is supported by *MSDS*^{3D} (72, 73).

For *MSDS*^{3D}, drug-specific modules have been developed based on the proposed handling of the specific MS treatment (74, 75). The natalizumab module, specifically adapted for treatment with the monoclonal antibody natalizumab, contains all essential process components from the indication to the infusion procedure and the necessary control tests. The sequence of the visits and the instruments to be filled in are defined in the *MSDS*^{3D} natalizumab module. Subsequent instruments include disease history, EDSS, and MSFC as well as MRI and para-clinical parameters as lab data.

Specifically, a checklist was integrated that asks for the occurrence of common symptoms associated with progressive multifocal leukoencephalopathy (PML) as a possible side effect of natalizumab therapy and must be answered by each patient alone or in the presence of relatives before each infusion. This is also done via touch screen on the patient terminal or via touch pad. If the checklist contains warnings of a PML, so-called red flags appear, which require an immediate patient consultation with the attending physician. Once all the instruments necessary for the respective visit have been performed, the physician approves the infusion and only then can natalizumab be administered. The infusion itself is documented by the nurse who also arranges the next appointment using the MSDS^{3D} appointment manager. If the patient does not appear at the agreed appointment, the nurse and doctor are reminded by *MSDS*^{3D}. If all instruments of therapy with natalizumab are marked green, the visit can be verified with the appropriate authorization and transferred to a central register (e.g., MS register or drug-specific register) in a pseudonymized manner. Compliance with the applicable national and European data protection regulations is guaranteed.

The findings from this pilot project are widely applied throughout Germany in the TRUST study initiated by Biogen to accompany patients under treatment with natalizumab (76). In addition, other modules have been developed to collect data of high-efficacy treatments with fingolimod (77, 78) and alemtuzumab (79). For alemtuzumab, *MSDS*^{3D} provides the necessary regular monitoring to ensure clinical vigilance after completion of the infusion courses over the necessary observation period of 4 years. It enables cross-sectoral standardized management and documentation of patients treated with alemtuzumab and can serve as a data entry system for various databases. We successfully linked clinical and imaging data of individual patients with the promising biomarker serum neurofilament light in Alemtuzumab-treated patients (80). For ocrelizumab, the CONFIDENCE study was integrated into the *MSDS*^{3D} platform as a large, non-interventional PASS that assesses long-term safety and effectiveness of Ocrelizumab and other MS treatments in comparison (81). Interestingly, these data will be integrated into other studies that have been developed to fulfill international regulatory requirements (EMA, FDA). Cladribine data are collected using the CLARION *MSDS*^{3D} module in Germany.

Additionally, *MSDS*^{3D} has found its way into the implementation of various scientific research projects as, for example, the multicenter study "Responsiveness of patient based outcome parameters in MS" (REPABO), in which pwMS were followed over up to 3 years and patients and their study physician rated different scales in parallel each year (82). A new physician tool, MSProDiscuss, was integrated in the PANGAEA module to facilitate physician–patient discussion in evaluating early, subtle signs of disease progression that represent the transition from relapsing–remitting to secondary progressive subtype (83).

PERSPECTIVE

In the age of large, complex, digitally available data sets (big data), and the establishment of suitable analytical methods, MS as a widespread chronic disease with various characteristics is predestined for large-scale data research approaches (84, 85). There are many prerequisites for finally investigating origin, progression modifiers, and chances of remission in greater depth with modern analytical methods in larger cohorts: the not yet completely clarified etiology, complex constellations of symptoms, the growing register landscape, as well as newly emerging markers and progression approaches (3, 33, 36). Big data analyses (e.g., data mining and machine learning) will not turn MS into a curable disease, but clear application goals can be derived:

- Comprehensive automated analysis of MRI data.
- Data-driven individualization of therapy recommendations.
- In real-time optimized follow-up by simultaneous consideration of numerous clinical outcomes and PROs.

- Combination of previously isolated domains such as genome, molecular, and epigenetic data.

Typical pitfalls of large complex data sets are potentially poor data quality, data inconsistency, poor data stability, securing patient protection and consent, and other legal barriers (13, 84, 86, 87). In addition, the interpretability of the results must be in the foreground when research moves away from the level of confirmatory hypothesis testing in order not to achieve irrelevant or misleading results. Ultimately, findings from big data have to be elaborated into new testable hypotheses. However, the data-oriented perspective also strengthens the view of the actual effect sizes (clinical important differences), where up to now all significant *p*-values of certified minimum effects have been too often classified as relevant.

Data from multiple sources such as registries, EMRs, and PASS can be separately analyzed and combined in a meta-analysis or brought together in a single big data source for MS research like the MS Data Alliance (13, 33). As we have described above, *MSDS*[3D] has enabled us to free data sources, data collection systems, and study types from their pigeonholes in an integrative manner by building a system that already integrates data from registers, safety studies, and highly specialized EMR processes. Our vision is to provide a platform for holistic management of MS that allows parallel data collection for specific analysis.

Our next steps will be to include neurorehabilitation into this big data approach in MS by creating a neurorehabilitation module in MSDS[3D]. Here, too, we will follow the approach of making data collected as holistically as possible available to all participants in order to maintain multi-domain patient skills beyond isolated symptomatic approaches. On the professional side, the implementation of clinical pathways for the treatment of symptomatic disabilities will enable data-driven standardized care and make it measurable and verifiable (88). In our system, we have already implemented the necessary data to address, for example, motor deficits and psychosocial problems. We must now take these data and combine it with the efforts of doctors, nurses, and patients who already share and use parts of it. In this way, the electronically supported cycle of data from conception, collection, linking, and utilization can be completed.

AUTHOR CONTRIBUTIONS

TZ, RK, IV, and RH wrote the manuscript. All authors reviewed and approved the final manuscript.

FUNDING

The MSDS[3D] module development was supported by the Hertie Foundation, Novartis, Teva, Roche, Sanofi, Biogen, and Merck.

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Conflict of Interest: TZ, IV, RH declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. TZ received personal compensation from Biogen, Bayer, Celgene, Novartis, Roche, Sanofi, Teva for the consulting services and additional financial support for the research activities from Bayer, BAT; Biogen, Novartis, Teva, and Sanofi. RK is CEO of MedicalSyn GmbH. RH received personal compensation by Sanofi and travel grants by Celgene and Sanofi.

frontiers in Neurology

CLINICAL TRIAL
published: 31 July 2020
doi: 10.3389/fneur.2020.00671

Technical Features, Feasibility, and Acceptability of Augmented Telerehabilitation in Post-stroke Aphasia—Experiences From a Randomized Controlled Trial

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OPEN ACCESS

Edited by:
Simona Bonavita, University of Campania Luigi Vanvitelli, Italy

Reviewed by:
Alessandro Giustini, Istituto di Riabilitazione Santo Stefano, Italy
Annie Jane Hill, The University of Queensland, Australia

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Specialty section:
This article was submitted to Neurorehabilitation, a section of the journal Frontiers in Neurology

Received: *17 December 2019*
Accepted: *05 June 2020*
Published: *31 July 2020*

Citation:
Øra HP, Kirmess M, Brady MC, Sørli H and Becker F (2020) Technical Features, Feasibility, and Acceptability of Augmented Telerehabilitation in Post-stroke Aphasia—Experiences From a Randomized Controlled Trial. Front. Neurol. 11:671. doi: 10.3389/fneur.2020.00671

Background: Post-stroke aphasia is a communication disorder where existing evidence favors intensive therapy methods. Telerehabilitation represents a service model for geographically remote settings, or other barriers to clinic attendance or to facilitate an augmentation of therapy across a continuum of care. Evidence to support efficiency, feasibility, and acceptability is however still scarce. Appraising aphasia telerehabilitation in controlled trials beyond its effectiveness, by investigating feasibility and acceptability, may facilitate implementation into clinical practice.

Methods: In our pilot randomized controlled trial, we investigated the feasibility and acceptability of speech and language therapy by videoconference, in addition to usual care, in people with aphasia following stroke. To improve functional, expressive language, a tailored intervention was given 1 h per day, five times per week over four consecutive weeks. Feasibility measures included evaluation of technical setup using diary logs. Acceptability was investigated by examining adherence and satisfaction with therapy alongside evaluation of data safety and privacy.

Results: Feasibility and acceptability data were collected in relation to 556.5 h of telerehabilitation delivered to 30 participants over a 2-years intervention period by three speech-language pathologists. Protocol adherence was high, with a tolerable technical fault rate; 86 faults were registered over 541 video sessions. Most (80%; $n = 30$) of the participants experienced zero to three faults. The main cause of technical failures was flawed internet connection, causing delayed or interrupted therapy. Total satisfaction with telerehabilitation was rated good or very good by 93.1% ($n = 29$) of participants and two of three speech-language pathologists. Within a moderate variance of technical failure, participants experiencing more faults were more satisfied. No serious events regarding security and privacy were reported. Our model is feasibly and ready to be implemented across a range of clinical settings and contexts.

Conclusions: Synchronous telerehabilitation for post-stroke aphasia is feasible and acceptable and shows tolerable technical fault rates with high satisfaction among patients and pathologists. Within a low rate of faults, satisfaction was not negatively influenced by fault frequency. Access to clinical and technical expertise is needed when developing telerehabilitation services. Telerehabilitation may be a viable service delivery model for aphasia rehabilitation.

Trial Registration: ClinicalTrials.gov, ID: NCT02768922.

Keywords: aphasia, telerehabilitation, videoconference, stroke, feasibility

INTRODUCTION

Over the last decades, services enabled by information and communications technology (ICT) have embodied a paradigm shift in the healthcare sector, where its use to increase both efficiency and accessibility of services is clearly advocated in the literature (1). In addition, the use of ICT has enabled the development of telerehabilitation, an emerging model to provide services in several disciplines of rehabilitation medicine (2, 3). In countries like Norway, with its extensive rural regions and long distances to healthcare facilities, telerehabilitation represents a flexible, low-cost, and innovative way to provide, optimize, and enable rehabilitation for different kinds of disabilities. With the use of telerehabilitation, we may provide services for those experiencing challenges in attending clinical appointments, like patients with decreased motor function and/or fatigue following stroke.

One condition that seems suitable for telerehabilitation is aphasia (4). Aphasia is a disorder seen following stroke or other causes of acquired brain injuries as a result of damage to the language-dominant hemisphere of the brain. People with aphasia may have different degrees of multimodal language impairment, like deficits in spoken language, auditory comprehension, reading, and writing. In acute stroke, aphasia is seen in a third of all cases (5) and is a predictor for outcomes in recovery (6, 7). Rehabilitation of people with aphasia is thus of importance, where existing evidence favors intensive therapy methods (8, 9).

In today's rehabilitation services, intensive aphasia rehabilitation is often not provided due to restricted resources and an uneven geographical distribution (10). In this context, speech and language therapy by videoconference represents an alternative route to make therapy more accessible in underserved and remote areas, or to accommodate the need for greater therapy dosage. In recent years, studies on aphasia telerehabilitation using both synchronously (real-time) and asynchronously (delayed) approaches have been conducted (11, 12). Customized internet videoconferencing technology offers much promise to aphasia services, with studies supporting speech and language therapy by videoconference as a viable alternative in both individual one-to-one sessions (13–15) and group-based interventions (16, 17).

Many projects involving new technology in the healthcare sector fail to reach full-scale trials or implementation into routine clinical practice (1, 18). With many promising pilot studies on aphasia telerehabilitation supporting future service delivery models, there is a need to gain more knowledge to overcome potential "pilotism." "Pilotism" is a term used to describe how many projects involving ICT remain as projects (1), which also seems to apply to the relatively new field of aphasia telerehabilitation as most studies to date have tended to be small. We need to gather and report the feasibility of the technical features, data safety aspects, and satisfaction in larger, controlled trials to facilitate implementation into clinical services.

Existing literature within the field of telerehabilitation and telehealth highlights the importance of applying human factors in the development of telemedicine services. In creating a telerehabilitation intervention, knowledge about the characteristics of the chosen population is necessary in order to select a technology that is consistent with users' needs, skills, and contexts, thus overcoming potential barriers in using the technology (19). People with aphasia following stroke represent a heterogeneous population, where additional components like cognitive deficits, visual impairment, reduced motor function, and the presence of language impairments might interfere with their use of technology. Hence, it is vital to be able to tailor telerehabilitation services toward the targeted population of people with aphasia, exploring barriers and facilitators by including the human factor.

We investigated speech and language therapy delivered by videoconference in addition to usual care in a randomized controlled trial (RCT). The overall objective of our trial was to explore whether augmented telerehabilitation for aphasia post stroke is effective, feasible, and acceptable (20). The effect of our intervention on language outcomes has been reported elsewhere (21). The aim of this article is to describe our technical setup, including the choice of software, hardware, and our procedure for the installation of technical equipment together with user instructions. We will further present our findings in relation to feasibility and acceptability including evaluation of safety, privacy, and confidentiality. Our results consist of reports on participants' experience and data collected in relation to 556.5 h of one-to-one sessions of speech and language therapy delivered through videoconference.

METHODS AND MATERIALS

We conducted a pragmatic RCT, where augmented telerehabilitation for people with aphasia following stroke

was explored (20). Participants were randomly allocated to a parallel group design to receive telerehabilitation in addition to usual care (telerehabilitation group) or to usual care alone (control group). The protocol has received ethical approval by the Norwegian Regional Committee South East for Medical and Health Research Ethics (Approval number 2015/2129) and is registered at the Clinical Trials Government (NCT02768922).

Participants

The participants that received the telerehabilitation intervention represented a relatively unselected sample from a clinical population of people with aphasia following stroke, as broad inclusion criteria were endorsed. Participants with no limits concerning time post stroke or previous history of stroke and with Norwegian as their main language were enrolled. Participants had impairments in several language modalities, though our inclusion criteria specified naming deficits as our therapy intervention focused on spoken language. Only candidates that could not comply with the telerehabilitation intervention due to medical and/or cognitive causes were excluded.

Participants were identified and recruited from Sunnaas Rehabilitation Hospital, other rehabilitation institutions, cooperating local speech-language pathologists, and stroke units at four hospitals in the Oslo area. The research investigator (HØ) made an ambulatory visit to the participant's location for enrolment and to gain informed consent. Written informed consent was obtained from all participants and from the speech-language pathologists who delivered the telerehabilitation.

Telerehabilitation Intervention

The Sunnaas Rehabilitation Hospital has extensive experience in the rehabilitation of patients with aphasia and the use of telemedicine and benefits from the input of a specialist telemedicine team who support the integration of telemedicine in ordinary clinical routines (22, 23). The current project was thus developed in an already well-established organizational setting with clinicians and technicians with substantial knowledge of the targeted population and wide experience from earlier and ongoing telemedicine projects. In addition, applicable components of the American Telemedicine Association's Principles for Delivering Telerehabilitation Services (24), adjusted to a Norwegian context, were integrated in our aphasia telerehabilitation project.

In our RCT, adaptations and strategies were used to increase user-friendliness and accessibility and furthermore modify the telerehabilitation to the selected patient group. The technical solution was modeled through an earlier, smaller feasibility study where personalized speech and language therapy was delivered through videoconference to four people with aphasia (25). The feasibility study identified elements in the technical arrangements requiring improvement, supporting the scaling-up of the intervention to a larger trial. Our final chosen technical setup was piloted on inpatients at Sunnaas Rehabilitation Hospital before recruitment started to our pilot trial. The telerehabilitation was delivered via videoconference from Sunnaas Rehabilitation Hospital to the participant's location (own home, institution, and rehabilitation ward). Each therapy session started with the speech-language pathologist connecting to the participant's computer by videoconference and remote-control software. After the connection was established, a "start-up" checklist (**Supplementary File 1**) was used at the start of each session to ensure optimal settings, privacy, and security.

The dose of the telerehabilitation intervention was 1 h per day, five times per week over four consecutive weeks. For some participants, therapy was delivered in slightly longer sessions over a smaller number of times per week, still providing the same total dosage of 20 h of telerehabilitation. The telerehabilitation was given with the intensity of 5 h per week, as this was in accordance with Norwegian national guidelines. Regarding the content of the speech and language therapy, a mixed theoretical approach was applied that included different impairment-based methods (e.g., functional-orientated and cognitive–linguistic methods). The therapy was further tailored to the participant's language impairment by both functional relevance and difficulty level, across all language modalities with a special focus on functional expressive communication. The Template for Intervention Description and Replication (TIDieR) Checklist was used to ensure transparency and replicability for future studies and to facilitate clinical implementation (20, 26).

Hardware

Participants were provided with a portable Fujitsu PC (laptop) with necessary software and material for the intervention installed. The setup further involved a portable Jabra speakerphone to improve sound quality and a Logitech C930e webcam with a wide 90° field of view, both designed to support videoconferencing. The wide-angle web camera enabled the speech-language pathologist to see the patient's upper body, allowing the participant to use alternative communication strategies, such as body language, and gestures. A wireless computer mouse facilitated participants' control of the pointer.

The speech-language pathologist also used a portable PC, with the same installation of material and software as in the participants' computers. Each speech-language pathologist's computer was further connected to a desktop videoconference system from the Cisco TelePresence System EX Series. To establish the videoconference sessions, existing internet connection at the respective local sites was used. Various kinds of hardware were applied to access the available internet (e.g., mobile internet devices, modems, internet routers, network cables). The connection between Sunnaas Rehabilitation Hospital and the participants' computers was through Norwegian Health Net's (NHN) encrypted video service, over standard, consumer level mobile or landline broadband. The speech-language pathologists used the hospital's ordinary local network (LAN), connected via cable or over WiFi.

Software

We used the videoconference software called Cisco Jabber/Acano from NHN. In addition, the speech-language pathologists used the software LogMeIn, which allowed them to override and remotely control the participants' computer if required. The

remote-control software had [during the first feasibility study (25)] proved to be a highly valuable tool, as it supported the participants and provided assistance with computer access and technical problems. This was especially appreciated among our participants who had aphasia and, in some cases, additional cognitive impairments, apraxia, and/or limited computer skills. They only needed to turn on the computer to connect and access therapy.

The laptops were equipped with a Windows operating platform comprising Microsoft office tools. The web browser Internet Explorer was installed to access training material on the internet like maps, pictures, and easy-to-read newspapers. Lexia, a language training software, customized to facilitate retraining of language skills in people with aphasia, was also set up on all computers. The videoconference software enabled the speech-language pathologists to share presentations and material from their own computer on the screen. The LogMeIn program also allowed the speech-language pathologists to remotely select material for each session directly on the participant's computer.

Evaluation of Security and Privacy

One of the keystones when using ICT in a healthcare services is a systematic valuation of possible threats to security and privacy, including data protection and confidentiality. In Norway, all electronic communication of personal information is regulated by national legislation, where identifiable health-related data are considered sensitive information (27). In this project, assessment of privacy and security aspects was done by a risk and vulnerability analysis (RVA) under direction of the hospital's Data Protection Office and in cooperation with the telemedicine team. The analysis was performed before the start of recruitment and under piloting of the technical setup.

The RVA indicated that there was sufficient protection of sensitive information and that the chosen technical setup adequately preserved privacy and confidentiality. The videoconference system used encrypted software and therapy sessions were live with no video recordings. Study laptops were utilized instead of participants' own computers, as LogMeIn could have enabled the speech-language pathologist to access potentially sensitive or private material. Other risk-reducing measures included completion of a "start-up" checklist at the beginning of each therapy session (**Supplementary File 1**). The checklist was developed as a tool to control and adjust the patient's physical environment, to optimize therapy, preserve privacy, and to confirm emergency contact details. In addition, all participants received their own user account in the videoconference software. Reuse of accounts was not endorsed. As the study laptops alternated among participants, cleaning and disinfection of the equipment using water and alcohol-based liquid or gel took place between each intervention and before delivering the equipment to the next participant. In addition, each computer was digitally cleaned and reset at the end of every intervention period to delete any used teaching material or sensitive information stored on the desktop during therapy sessions.

Installation of Technical Equipment and User Instructions

Following baseline testing, the principal investigator (HØ) set up the equipment at the participant's location where the telerehabilitation was to take place (e.g., own home, rehabilitation ward). If possible, the speech-language pathologist who was to deliver the intervention met the participant in person before therapy started, often during baseline assessment, to support the development of a good therapeutic alliance. If this meeting could not be arranged, the speech-language pathologist and the participants met "face to face" by videoconference during the installation of the equipment at the site.

Setting up the technical equipment included connecting the participants' portable computer to the internet at the local site. This involved testing out the videoconference connection to the investigator's laptop at the site or directly to the speech-language pathologists at Sunnaas Rehabilitation Hospital, if the speech-language pathologist was not taking part in installation. After the initial installation, the internet and the participant's computer connected automatically as soon as the computer was turned on. This enhanced ease of use. Providing an internet password to attend each video session was expected to be a challenging task for most of the participants.

After connection was established, the speech-language pathologist performed a demonstration to illustrate the therapy material and videoconference software. The principal investigator (HØ), responsible for the technical installations, remained with the participant during this demonstration to address any technical difficulties and provide training. Instructions for use of the computer and software were given. A manual on how to start up the computer and begin therapy sessions was handed out alongside the "start-up" checklist (**Supplementary File 1**). If possible, family members and/or caregivers were also invited to take part in the demonstration and provided with user instructions.

The speech-language pathologists that delivered the therapy by videoconference received personalized training adjusted to their clinical experience, computer skills, and practice in using videoconference systems (duration of training was on average ∼10 h). The training focused especially on how to use the chosen therapy materials in a telerehabilitation context, including how to use the equipment and selected software. Piloting with inpatients at Sunnaas Rehabilitation Hospital was performed in order to train the speech-language pathologists in delivering the speech and language therapy by videoconference. The technical training was given under the guidance of the telemedicine team, who also provided the necessary technical support during the intervention period. The telemedicine team consisted of both ICT personnel and clinicians with experience in the use of telerehabilitation.

Assessments of Feasibility and Acceptability

The evaluation and assessment of the intervention's feasibility and acceptability were continuous throughout the project period. An operational definition of the two terms was used to specify

TABLE 1 | The feasibility and acceptability measures.

Variable	Assessment tool	Description
Feasibility of the technical setup	User error/Technical failure log	Number of user errors/technical problems including where the error/fault occurred and consequence of the error/fault (delayed/interrupted or canceled session)
Acceptability:		
Data safety and privacy aspects	Risk and vulnerability analysis	Location of potential risks, assessment of their potential consequences and elaboration of risk-reducing measures
Adherence to intervention	Diary log	Drop-out rate and number of sessions completed
Satisfaction with intervention	Questionnaires and semi-structured interviews	Satisfaction with intervention on a five-point scale Semi-structured interviews with speech-language pathologists and selected participants (Not included in this paper)

which components to include in the objective measures to evaluate the telerehabilitation delivered. We defined acceptability as satisfaction with the telerehabilitation, adherence to the intervention involving withdrawal and dropout rate, and issues of privacy including safety and confidentiality. Feasibility compromised the viability of our chosen technical features like internet solution, software, hardware, and the videoconference system. The feasibility and acceptability measures are illustrated in **Table 1**.

Our feasibility evaluation contained assessments of technical solutions where failure and technical difficulties were charted. Beyond this, feasibility measures included evaluations of the ease of use of the chosen technical solution for the participants and the speech-language pathologists. To assess feasibility of the technical setup, a log designed as a technical failure registration form was developed. The speech-language pathologist filled out this log if technical challenges arose during a videoconference session. The technical failure registration form categorized where the fault seemed to have occurred and evaluated the consequence of the given fault (**Supplementary File 2**). User-friendliness of the technical setup was among others assessed by labeling if the failure was a single technical problem or a user error (e.g., a participant's difficulty using the computer, software, and/or technical equipment).

Acceptability was evaluated by questionnaire where each participant and speech-language pathologist were asked to rank satisfaction on a five-point scale (**Supplementary File 3**). At the end of the questionnaire, each person was given the opportunity to provide general feedback in writing to further explore their experiences with the telerehabilitation. The questionnaire for the participants was modified for people with aphasia, as aphasia-accessible formatting improves comprehension of written health information (28).

In addition to the abovementioned evaluation, semi-structured interviews with selected participants and the speech-language pathologists were performed to further explore the ease of use, perception, experience, and satisfaction with the telerehabilitation intervention. These qualitative data will later be coded, analyzed, and presented in subsequent publications.

Statistical Analysis

Statistical analysis was conducted using SPSS version 25.0 (IBM SPSS Inc., Chicago, IL, USA). Descriptive statistics were used to summarize clinical and demographic characteristics, features of the intervention, and the results of the questionnaires and technical log. In addition, descriptive statistics in the form of graphs and plots were used to explore links and relationships between various demographic variables and clinical variables toward technical feasibility and satisfaction with the therapy by videoconference. Demographic and clinical variables selected to investigate possible relationships were age, gender, auditory comprehension, and degree of disability in daily activities as measured by the modified Rankin Scale.

RESULTS

Feasibility and acceptability data were collected in relation to 556.5 h of speech and language therapy by videoconference delivered over a 2-years intervention period from May 2016 to June 2018. Thirty participants received speech-language telerehabilitation by videoconference in addition to usual care. The participants that received our intervention had impairments in several language modalities including naming, auditory comprehension, repetition, and the ability to produce sentences as measured by the subtest of the Norwegian Basic Aphasia Assessment (percentile score) (29) and the subtest sentence production from the Verb and Sentence Test (20 pictures with targeted sentences) (30). The Modified Rankin Scale (mRS) revealed various degrees of disability within the selected sample, where most participants were labeled as slightly or moderately disabled. The demographic and clinical characteristics of the participants including features of the telerehabilitation intervention are shown in **Table 2**.

FEASIBILITY

Technical Failure Registration Log

There were 86 faults registered during the intervention period, occurring in 85 of the total 541 video sessions provided. The technical problems were solved by using the LogMeIn software

TABLE 2 | Demographic and clinical variables including features of the telerehabilitation.

Variable	Participants who received telerehabilitation ($n = 30$)
Age in years, mean (SD)	64.4 (11.7)
Gender, *n* (%)	
Male	19 (63.3%)
Female	11 (36.7%)
Marital status, *n* (%)	
Married/cohabitating	22 (73.3%)
Widow/widower	3 (10.0%)
Single	5 (16.7%)
Housing conditions, *n* (%)	
Independent living without home care nursing	17 (56.7%)
Independent living with home care nursing	10 (33.3%)
Sheltered housing with 24/7 care services	2 (6.7%)
Nursing home	1 (3.3%)
Living situation *n* (%)	
Living alone	8 (26.7%)
Living with someone	21 (70.0%)
Nursing/institution	1 (3.3%)
Time from stroke onset in months, *n* (%)	
≤3 months	14 (46.7%)
3–12 months	5 (16.7%)
≥12 months	11 (36.7%)
Modified rankin scale at baseline, *n* (%)	
No significant disability	-
Slight disability	14 (46.7%)
Moderate disability	8 (26.7%)
Moderately severe disability	7 (23.3%)
Severe disability	1 (3.3%)
Language test at baseline, mean (SD)	
NGA naming—percentile	38.6 (13.9)
NGA comprehension—percentile	47.9 (20.4)
NGA repetition—percentile	39.9 (20.5)
VAST total score	7.6 (6.2)
Telerehabilitation intervention	
Hours of therapy by videoconference per participant (mean)	18.6
Duration of telerehabilitation intervention in days (mean)	27.6
Total hours of SLT by videoconference delivered in the trial	556.5
Total sessions videoconference in the trial	541
Location when receiving telerehabilitation intervention, *n* (%)	
Own home	20 (66.7%)
Rehabilitation ward/institution	5 (16.7%)
Own home and rehabilitation ward/institution	5 (16.7%)

NGA, Norwegian Basic Aphasia Assessment; VAST, Verb and Sentence Test, subtest sentence production; SLT, Speech-language therapy.

or by giving participants and/or family members/caregivers instructions over videoconference or telephone. The primary researcher (HØ) occasionally made ambulatory visits if these initial measures failed to resolve the technical issue (∼5–7 visits in total). The details of the technical failure registration log are described in **Table 3**.

Data from the log revealed a higher frequency of technical difficulties during the start of the trial, with fewer faults registered in later stages. Forty faults occurred in the first six participants, while faults registered in video sessions with the first 10 participants accounted for 70% of all failures (60 faults). The majority of the participants encountered thus a limited number of faults. Of all of the participants, seven did not have any faults registered in the technical failure registration log. Only six participants experienced more than three faults during their intervention period, where three of these six participants had more than seven faults (**Table 3**). The highest number of faults registered in a participant was 14.

The greatest cause for technical failures were problems with the internet connection. The log showed that there may have been an association between the type of internet service available in the local setting and the frequency of technical faults (**Table 3**). A Mobile 4G or Wi-Fi network within a formal institution seemed related to more technical difficulties, as 4G was used in 21.5% and Wi-Fi network in 19.2% of the sessions where faults were registered. 4G was the internet solution used most in video sessions due to its wide availability in Norway. The most frequent consequence of failures and technical difficulties, which delayed or interrupted therapy, was a reduction in quality in sound and picture due to unstable connectivity. Only 4 of the 541 video therapy sessions were canceled because of technical problems during the trial. As most of the faults were recorded as a single technical issue, the user-friendliness of the technical setup for the participants was considered adequate. When technical faults were studied using descriptive statistics regarding age, gender, auditory comprehension, and degree of disability in daily activities, no clear associations between variables were detected.

ACCEPTABILITY

Satisfaction With the Telerehabilitation Intervention

The questionnaires return rates reporting the telerehabilitation intervention experiences were good, as only one participant failed to respond ($n = 29$). Of the participants that completed the questionnaire, 93.1% rated their overall satisfaction with therapy as good or very good. Two of the three speech-language pathologists responded in the same way. In general, participants' scores were high on satisfaction for most items. Only one participant reported the experience as "bad," categorizing the sound and picture quality as bad. Among the speech-language pathologists, we saw a lower satisfaction rate compared to the participants as they used the response option "between good and bad" more frequently (from 33.3 to 67, 7%). One of the speech-language pathologists rated picture quality as "bad." Results regarding satisfaction are illustrated in **Table 4**.

In the last section of the questionnaire, the participants and the speech-language pathologists were given the opportunity to comment in general on how they experienced the received

TABLE 3 | Technical failure registration log and internet solutions.

Type of internet connection used in local settings, *n* (%)	
Mobile 4G network	3 (10%)
Wi-Fi network in institution	3 (10%)
Broadband DSL	5 (16.7%)
Broadband Cable	7 (23.3%)
Broadband Fiber	3 (10%)
Combinations of internet ($n = 9$):	
Wi-Fi network in institution + Mobile 4G network	4 (13.3%)
Wi-Fi network in institution + Broadband Fiber	1 (3.3%)
Broadband DSL + Mobile 4G network	3 (10%)
Broadband Fiber + Mobile 4G network	1 (3.3%)
Total number of sessions delivered by videoconference	541
Type of internet connection used in video sessions (% of total sessions)	
Mobile 4G network	144 (26.6%)
Wi-Fi network in institution	99 (18.3%)
Broadband DSL	118 (21.8%)
Broadband cable	128 (23.7%)
broadband fiber	52 (9.6%)
Type of failure	
Technical fault	83
User error	3
Total sum of failure registered during intervention	86
Amount of registered faults per participant, *n* (%):	
0	7 (23%)
1–3 faults	17 (57%)
4–7 faults	3 (10%)
8 or more faults	3 (10%)
Amount of registered faults per internet type (% of total faults)	
Mobile 4G network	32 (37.2%)
Wi-Fi network in institution	19 (22.1%)
Broadband DSL	17 (19.8%)
Broadband Cable	13 (15.1%)
Broadband Fiber	5 (5.8%)
Amount of sessions with faults per internet type (% of sessions per) internet type)	
Mobile 4G network	31 (21.5%)
Wi-Fi network in institution	19 (19.2%)
Broadband DSL	17 (14.4%)
Broadband Cable	13 (10.2%)
Broadband Fiber	5 (9.6%)
Where the faults occurred/cause of registered fault	
SLP's computer	3
LogMeIn software	3
Unknown origin	4
Videoconference equipment	6
Videoconference software	7
Participant's computer	8
Network connection	55
Consequence of the fault	
Delayed training session	29
Delayed and interrupted training session	53
Canceled training session	4

TABLE 4 | Experience and satisfactory with the delivered telerehabilitation intervention, *n* (%).

Question	Participants *n* = 29 (%)	Speech-language pathologists *n* = 3 (%)
1. How has it been like to receive/deliver speech-language therapy by video conference?		
Very bad	0	0
Bad	0	0
Neither good nor bad	2 (6.9)	1 (33.3)
Good	13 (44.8)	1 (33.3)
Very good	14 (48.3)	1 (33.3)
2. Were you satisfied with the video quality?		
Very bad	0	0
Bad	1 (3.4)	1 (33.3)
Neither good nor bad	3 (10.3)	2 (66.7)
Good	13 (44.8)	0
Very good	12 (41.4)	0
3. Were you satisfied with the sound quality?		
Very bad	0	0
Bad	1 (3.4)	0
Neither good nor bad	4 (13.8)	1 (33.3)
Good	13 (44.8)	1 (33.3)
Very good	11 (37.9)	1 (33.3)
4. Did you experience that your/the participant's language function improved by the speech-language therapy?		
Very bad	0	0
Bad	0	0
Neither good nor bad	5 (17.2)	1 (33.3)
Good	18 (62.1)	1 (33.3)
Very good	6 (20.7)	1 (33.3)
5. Overall, how satisfied are you with the language therapy that was received/delivered?		
Very bad	0	0
Bad	0	0
Neither good nor bad	2 (6.9)	1 (33.3)
Good	13 (44.8)	2 (66.7)
Very good	14 (48.3)	0

or delivered telerehabilitation. Fourteen of the participants gave feedback in their own writing or with support from family members. These comments were mainly on how the telerehabilitation intervention was perceived. Only one comment referred to technical features (which type of internet connection enabled the best sound). Feedback was also given on how the language training was regarded as good, useful/helpful, challenging, or educational. One participant reported that initially the therapy was tiring, but delivered great benefit in the end. Another participant considered the telerehabilitation received, augmenting their usual care, as a big advantage. One family member reported that the participant had become more positive and self-confident as a consequence of their participation. Involvement in the trial was described to facilitate the use of the Lexia program for self-training

in addition to other therapy and greater participation in functional conversation. Several users wished to continue with speech and language therapy by videoconference after the intervention period.

The speech-language pathologists commented on how the stability in the internet connection affected the quality of the picture and sound, and how poor sound and picture quality had a negative effect on the therapy. Benefits of the delivery mode were reported, including how the therapy was time-efficient and energy-saving. One comment referred to how the intervention could be further developed, with suggestions to add utilities for training writing skills by hand. Writing was only possible by keyboard in the current setting. The wish to continue to use this form of therapy in combination with more traditional face-to-face treatment was also expressed.

In summary, there seemed to be little relationship between the amount of technical failures and satisfaction with the speech and language therapy by telerehabilitation. Participants with a high frequency of technical faults still reported overall satisfaction with the intervention. The data revealed that within a moderate variance of fault rates, patients experiencing more faults were more satisfied (**Figure 1**). When data on satisfaction were systematically analyzed with regard to age, gender, auditory comprehension, and degree of disability in daily activities, no clear associations were detected. There might however have been a stronger connection between technical difficulties and satisfaction in the speech-language pathologists. Technical difficulties were reported by the speech-language pathologists as both challenging and frustrating, as well as having negative impact on the quality of language rehabilitation provided.

Security, Privacy, and Adherence to the Intervention

The overall attendance at scheduled videoconference sessions was good. The protocol aimed at 20 h of speech and language therapy by videoconference over four consecutive weeks (5 h of therapy per week). To ensure a sufficient therapy time as defined per protocol, the participants were required to complete $\geq$16 h of speech and language therapy over 32 days. All 30 participants that received the intervention met this requirement. Most participants received speech and language therapy 60 min per day, 5 days per week over 4 weeks. In some cases, more prolonged therapy time (70–120 min per session) was given over fewer days to meet participant's broader stroke rehabilitation schedule. Hours of therapy by videoconference delivered per participant were 18.6 h (mean) over a duration of 27.6 days (mean), indicating a high acceptability and adherence to the intervention protocol. No participant withdrew during the delivery of the telerehabilitation intervention. Risk-reducing measures were successfully implemented in the protocol. Throughout the trial, no serious or adverse effects, or breaches in security, privacy, or confidentiality were reported.

DISCUSSION

In this study, we explored feasibility and acceptability of augmented speech and language therapy delivered by videoconference. We found high adherence to the trial protocol. All 30 participants completed the intervention per protocol requirements. There was a tolerable fault rate, as the majority of the participants experienced no or only a limited number of faults. Most faults occurred in the early stages of the trial.

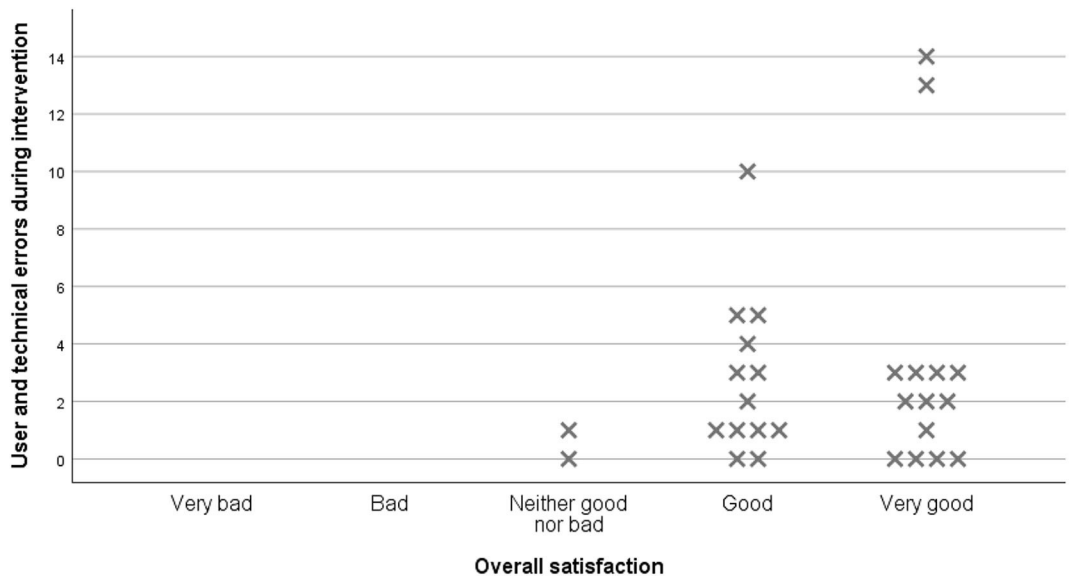

FIGURE 1 | Overall satisfaction in relation to technical faults and user errors.

Technical problems caused delayed or interrupted therapy and a reduction in the quality of sound and/or picture. The main source of technical faults was the internet connection. Satisfaction with the delivered telerehabilitation was high among the participants, but somewhat lower among the speech-language pathologists. Adequate risk-reducing measures were implemented in the protocol and no serious breaches regarding security, privacy, or confidentiality were reported.

In the development of our telerehabilitation intervention, we identified several factors useful for future studies and clinical implementation of telerehabilitation. Our broad multidisciplinary team included both clinical and technical expertise and was essential to the development and delivery of a high-quality feasible technology-based intervention. In our study, the technical setup and content of the telerehabilitation intervention were developed collaboratively with ICT personnel experienced in the development and delivery of telemedicine projects. The project group also consisted of clinicians with expertise in the highly heterogeneous population of people with aphasia following stroke, which enabled important human factors to be acknowledged in our targeted sample: older people with potentially poorer digital literacy, language impairments, and possible visual and cognitive deficits. The most appropriate hardware and software for this population were identified and integrated within the technical setup, with the goal to create a technical solution that was easy to use and easy to access while preserving privacy and security. The final technical setup and intervention was the result of a long process of tailored, adaptation and piloting of an intervention clinically tested within a feasibility study prior to delivery within this larger pilot RCT. In our view, extended knowledge of both the patient group and technology was a key factor to the success of our pilot study. Dynamic development of the intervention based on multidisciplinary expertise and competencies was essential to the development of a sustainable delivery model and is an experience that future development studies and trials may draw upon.

Another strength to be highlighted is our project's pragmatic nature, which preserves the exploration of feasibility and acceptability of the intervention within local and clinical contexts. The intervention was given to a relatively unselected, heterogeneous sample of the population of people with aphasia after stroke. Earlier, we highlighted this as a challenge in evaluating the efficiency of telerehabilitation on language outcomes (21). With regards to assessment of feasibility and acceptability measures, however, we achieved a greater ecological validity by endorsing broad, clinically relevant patient participant inclusion criteria. Similarly, our telerehabilitation intervention was delivered by practicing speech and language pathologists in a clinically relevant context. Our results highlight the important benefits of adopting a pragmatic design for other studies where new rehabilitation technology is explored. Such an approach facilitates clinical implementation, as knowledge about the feasibility and acceptability of the delivery of the technology within a clinical context, among a clinically relevant population and workforce, is essential for the development of clinically useful telerehabilitation interventions.

Feasibility of our technical setup could be improved as internet instability affecting connectivity was identified as the main reason for documented technical problems. Earlier studies on aphasia telerehabilitation have identified stable bandwidth connection as imperative in ensuring that telerehabilitation services are not negatively influenced by distortions in video or audio (31). In the work by Woolf et al. (14), videoconferencing was provided by FaceTime on Macs/iPads, a videoconference software currently not permitted in healthcare services in Norway due to information security regulations. In their study, Woolf et al. reported self-ratings on the quality of technology and transmission as high. However, there appeared to be no systematic logging of technical failures, giving little indication how often picture or sound were affected by connectivity problems. In a trial by Pitt et al. (16), constraint-induced language therapy was delivered by videoconference via the Adobe connect software. In this study, the technology log revealed a number of issues with connectivity, resulting in disconnection of video and/or audio. In another study using the same setup (17), technical-related issues were reported in all treatment sessions, and in some sessions, considerable time was spent resolving technical problems. Thus, our results confirm those from earlier studies that ensuring optimal connectivity by providing sufficient internet solutions is crucial when delivering synchronous aphasia telerehabilitation. This is applicable for all forms of synchronous telerehabilitation. With regard to telerehabilitation, future technological development providing more stable and sufficient internet solutions would be especially useful. It seems to be important to document and report on technical issues in telerehabilitation research, as done in this pilot trial.

In Norway today, 9 in 10 Norwegians between 16 and 79 years use the internet on a daily basis (32). Internet usage has grown rapidly over the last decades, where we have seen an increase in number of households subscribed to broadband together with a continuous rise in median internet speed throughout the country (33). As information on the current internet market in the trial's geographical setup suggested an adequate infrastructure, and in the context of our pragmatic trial, we decided to rely on internet solutions available in the participants' local settings. Our results suggest however that the established infrastructure may not always comply with the demands needed to deliver high-quality live videoconferencing. The number of devices and people using the network simultaneously during treatment sessions (peak internet usage times), together with other factors like reduced signal in brick buildings and large distance to router, may have influenced connectivity. As our video sessions were live, demands on internet quality, capacity, and speed were higher compared to other streaming activities.

In hindsight, closer evaluation of the internet solution in each setting could have been performed before the start of therapy. Assessment of internet connection quality could have been integrated in the protocol to a greater extent to safeguard optimal connection for the videoconference. In addition, the technical log did not contain measures of median Mbit/s. Though difficult to monitor, information on median Mbit/s could have

been used to map network data transfer rates vital to provide optimal video sessions.

Technical difficulties were highest in the trial start and declined during the course of the investigation. This has also been reported previously in other videoconferencing trials (34). This indicates that projects involving ICT go through a dynamic process that adds to an already complex intervention. Thus, there might be a need for an even longer piloting period than in more traditional RCTs. This should be considered when planning studies on telerehabilitation interventions. An important key factor to aid technical problems in our trial was the remote-control software. The LogMeIn software was a highly valuable tool to endorse ease of use and assist with technical challenges. We suspect that its use had a positive effect on satisfaction in both the participants and the speech-language pathologists in our study. We recommend the use of a remote-control software especially for patient groups with cognitive or communication impairments as it enhances acceptability when technical support can be provided remotely by both therapist and technicians.

High rates of satisfaction in combination with few user-related errors indicate high acceptability of our intervention. The non-physical presence of the speech-language pathologist during sessions was not explicitly examined in our questionnaire on satisfaction. This was however not a frequent topic mediated during conversation with participants, but could be interesting to further investigate in the future.

When analyzing the data, there seems to be little relation between the number of technical failures and participants' satisfaction. In general, a high degree of satisfaction with the technology was reported in the questionnaire (**Table 4**). This conforms with the earlier referred studies, where problems with connectivity were well-tolerated (14) and high satisfaction with technology was noted, despite problems with the transmission logged (16). In our trial, participants that experienced faults more frequently actually reported higher satisfaction levels. This might be a result of participants anticipating a level of technical difficulties and a variation of connectivity. The analysis of our qualitative data might shed further light on these results.

The speech-language pathologists' satisfaction ratings were somewhat lower as they reported poor sound and video quality, negatively affecting the quality of the training. As the SLPs provided many hours of therapy to different participants, they gained a broader picture of the delivered intervention and technical setup than the participants. This may have guided their ratings. In addition, it is also important to acknowledge that SLPs perform a number of tasks when delivering telerehabilitation as they handle technical challenges simultaneously with providing therapy. This may lead to higher requirements in the SLPs compared to the participants. There is a need to explore this further, also because the current sample is limited.

It is expected that future stroke rehabilitation services will increasingly integrate technology in therapy and training compared to today's services. There is a need for innovative thinking as an aging population, increased survival rates following stroke, and increasing fiscal constraints will demand healthcare resources beyond existing capacity in most countries. In our current trial, speech and language therapy by videoconference successfully augmented therapy time with a significant impact and effect on language outcomes for people with aphasia post stroke (21). Future trials should also investigate the possibility of telerehabilitation as a replacement to traditional face-to-face aphasia therapy, including effects on language function, patient and therapist experiences, tolerance to high-intensity interventions, as well as economical aspects. Further, comparative studies of different types of telerehabilitation (e.g., videoconferencing vs. asynchronous aphasia telerehabilitation) should be performed. While videoconferencing as a synchronous telerehabilitation method allows frequent direct contact with the speech-language pathologist as well as therapist-guided language training at home, asynchronous methods add flexibility for the patient and can further augment therapy intensity. Also, especially in the light of potential issues associated with connectivity instability, the use of hybrid approaches might be useful as, e.g., used in speech treatment for Parkinson's disease (35). Future research also needs to address whether particular telerehabilitation methods are more or less beneficial and acceptable for particular subgroups of people with aphasia, and how combinations of therapy delivery models might be optimized for the benefit of the patient.

In the new world of telerehabilitation, this study highlights the extra complexity that ICT adds to a rehabilitation intervention. An extended multidisciplinary approach where clinicians and ICT personnel work collaboratively was essentially for the development of our successful intervention and is thus recommended for future work in this field. In addition, efforts to establish optimal internet settings and solutions may inquire a greater cooperation with internet service and videoconference system providers. The demands of live videoconferencing on an internet connection are also important considerations in future trials and in the implementation of future clinical services.

Despite these challenges, our key findings suggest that telerehabilitation for aphasia may be a viable future service delivery model. Our pilot trial results suggest that our current intervention improves language functions and is acceptable to a clinically relevant patient group and therapists with high satisfaction rates. We consider this model ready to be implemented and evaluated on a larger scale and across different clinical contexts.

DATA AVAILABILITY STATEMENT

The datasets generated for this study will not be made publicly available. The dataset for this article is not publicly available because of Norwegian law regarding information privacy. Excerpts of the data can be made available on requests to the corresponding author.

ETHICS STATEMENT

This study involving human participants was reviewed and approved by Norwegian Regional Committee South East for

Medical and Health Research Ethics. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

HØ is a Ph.D. fellow and the principal investigator of the study. She contributed to the protocol design, performed statistical analysis, and drafted this manuscript. FB conceived the study and is the project manager and main supervisor for the project. MK and MB are co-supervisors. FB, MK, MB, and HS contributed to the design of the protocol, the conduction of the study, and the writing of this manuscript. All authors read and approved the final manuscript.

FUNDING

The trial was funded by the South-Eastern Norway Regional Health Authority (project number 2015037) and has received financial support from the University of Oslo and Sunnaas Rehabilitation Hospital. The NMAHP RU and MB are supported by the Chief Scientist Office, part of the Scottish Government Health and Social Care Directorates. The views expressed here are those of the authors and not necessarily those of the funders.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2020.00671/full#supplementary-material

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Neurology

ORIGINAL RESEARCH
published: 07 August 2020
doi: 10.3389/fneur.2020.00632

Harnessing Real-World Data to Inform Decision-Making: Multiple Sclerosis Partners Advancing Technology and Health Solutions (MS PATHS)

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Background: Multiple Sclerosis Partners Advancing Technology and Health Solutions (MS PATHS) is the first example of a learning health system in multiple sclerosis (MS). This paper describes the initial implementation of MS PATHS and initial patient characteristics.

Methods: MS PATHS is an ongoing initiative conducted in 10 healthcare institutions in three countries, each contributing standardized information acquired during routine care. Institutional participation required the following: active MS patient census of ≥500, at least one Siemens 3T magnetic resonance imaging scanner, and willingness to standardize patient assessments, share standardized data for research, and offer universal enrolment to capture a representative sample. The eligible participants have diagnosis of MS, including clinically isolated syndrome, and consent for sharing pseudonymized data for research. MS PATHS incorporates a self-administered patient assessment tool, the Multiple Sclerosis Performance Test, to collect a structured history, patient-reported outcomes, and quantitative testing of cognition, vision, dexterity, and walking speed. Brain magnetic resonance imaging is acquired using standardized acquisition sequences on Siemens 3T scanners. Quantitative measures of brain volume and lesion load are obtained. Using a separate consent, the patients contribute DNA, RNA, and serum for future research. The clinicians retain complete autonomy in using MS PATHS data in patient care. A shared governance model ensures transparent data and sample access for research.

Results: As of August 5, 2019, MS PATHS enrolment included participants (n = 16,568) with broad ranges of disease subtypes, duration, and severity. Overall,

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Edited by:
Marcello Moccia, University of Naples Federico II, Italy

Reviewed by:
Pietro Iaffaldano, University of Bari Aldo Moro, Italy
Kimberley Allen-Philbey, Barts Health NHS Trust, United Kingdom

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Specialty section:
This article was submitted to Neurorehabilitation, a section of the journal Frontiers in Neurology

Received: *20 December 2019*
Accepted: *28 May 2020*
Published: *07 August 2020*

Citation:
Mowry EM, Bermel RA, Williams JR, Benzinger TLS, de Moor C, Fisher E, Hersh CM, Hyland MH, Izbudak I, Jones SE, Kieseier BC, Kitzler HH, Krupp L, Lui YW, Montalban X, Naismith RT, Nicholas JA, Pellegrini F, Rovira A, Schulze M, Tackenberg B, Tintore M, Tivarus ME, Ziemssen T and Rudick RA (2020) Harnessing Real-World Data to Inform Decision-Making: Multiple Sclerosis Partners Advancing Technology and Health Solutions (MS PATHS). Front. Neurol. 11:632. doi: 10.3389/fneur.2020.00632

14,643 (88.4%) participants contributed data at one or more time points. The average patient contributed 15.6 person-months of follow-up (95% CI: 15.5–15.8); overall, 166,158 person-months of follow-up have been accumulated. Those with relapsing–remitting MS demonstrated more demographic heterogeneity than the participants in six randomized phase 3 MS treatment trials. Across sites, a significant variation was observed in the follow-up frequency and the patterns of disease-modifying therapy use.

Conclusions: Through digital health technology, it is feasible to collect standardized, quantitative, and interpretable data from each patient in busy MS practices, facilitating the merger of research and patient care. This approach holds promise for data-driven clinical decisions and accelerated systematic learning.

Keywords: learning health system, multiple sclerosis, MS PATHS, digital health technology, standardized brain magnetic resonance imaging

INTRODUCTION

The multiple sclerosis (MS) treatment landscape has experienced a dramatic evolution over the past two decades; there are now 16 approved disease-modifying therapies (DMTs). Approaches to personalized medicine in MS, however, have not kept pace. Defining disease prognosis, treatment outcomes, monitoring treatment response, and determining optimal treatment sequencing remain variable and somewhat subjective in MS practice. Personalized medicine efforts have focused both on identifying informative patient phenotypes (1) and effectively integrating and visualizing individual patient data (2).

The rigorous collection and analysis of real-world data may accelerate the development of personalized medicine in MS and address some of these gaps (3–5). Opportunities and challenges related to data pooling and data standardization in MS were recognized by early pioneers, beginning decades ago (6, 7), and recent progress has been summarized (8, 9). These efforts have ushered in an era of data standardization and pooling in an attempt to extend systematic learning beyond structured research protocols to more representative real-world populations. For maximum impact, data should include standardized and quantitative clinical, radiologic, and biological phenotyping from a heterogeneous population representative of the diversity of patients with MS seen in everyday clinical practice.

The learning health system (LHS) model, as proposed by the Institute of Medicine, outlines a method to enable broad-scale quantitative patient phenotyping through the merging of clinical research and healthcare delivery (4, 10). The LHS (also known as evidence-generating medicine) seeks to produce better outcomes and research based on real-time data acquisition (10). The tenets of the LHS concept include collection of standardized, meaningful data on every patient seeking care, increased engagement of patients in the process of care, use of quantitative data for clinical decision-making, and aggregation of data from populations for systematic learning (10). The LHS represents a culture of continuous learning, feeding insights back into care delivery to continuously reanalyze, revalidate, and improve outcomes.

The current report describes the first LHS in MS, Multiple Sclerosis Partners Advancing Technology and Health Solutions (MS PATHS). In MS PATHS, quantitative clinical and imaging data are collected in a standardized manner for each patient as part of routine care. Data are collected as part of the patient's clinical evaluation, while—with a patient's permission—the data are pseudonymized and aggregated for systematic learning. The program leverages technology and patient engagement to automate data collection and analysis, minimizing the burden on the care system and providers. The specific goals of MS PATHS are to better understand the disease, identify the predictors of therapeutic responses, define and measure outcomes during the course of care, and develop approaches to personalized medicine.

We aim to demonstrate the feasibility of implementing the key features of an LHS in MS by describing the patient population enrolled in MS PATHS to date, initial data completion rates, differences between MS PATHS and typical MS clinical trial patients, heterogeneity of practice across the network, and utilization of the research data.

Abbreviations: DMT, disease-modifying therapy; EMR, electronic medical record; FLAIR, fluid-attenuated inversion recovery; IQR, interquartile range; IT, information technology; LHS, learning health system; MPRAGE, magnetization-prepared rapid gradient-echo imaging; MRI, magnetic resonance imaging; MS, multiple sclerosis; MS PATHS, Multiple Sclerosis Partners Advancing Technology and Health Solutions; MSPT, Multiple Sclerosis Performance Test; NA, not applicable; Neuro-QoL, Quality of Life in Neurological Disorders; PPMS, primary progressive multiple sclerosis; PRMS, progressive relapsing multiple sclerosis; RCT, randomized controlled clinical trial; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis.

MATERIALS AND METHODS

Initial Design

MS PATHS is a collaborative network of healthcare institutions that have standardized elements of their clinical assessments and collaborated with Biogen to implement a centralized database for research purposes. This network was designed based on the guiding principles described in **Table 1**. In 2014, a group of stakeholders from Cleveland Clinic, Johns Hopkins University,

TABLE 1 | Guiding principles for MS PATHS.

Engage all healthcare providers and nearly all patients with MS in a healthcare institution
Standardize, quantify, and maximize data collected as part of standard of care • Identify key data points needed to interpret test results, achieve practice standards/meaningful use, and enable the generation of new clinical knowledge
Leverage technology to enable data collection in clinical practice • Make it possible to collect data on all participating patients, which is too time consuming using traditional research methods • Leverage patient-reported data to the greatest extent possible • Make MSPT data available at the point of care and simultaneously aggregate data for learning
Collect data outside of standard of care *via* separately consented substudies
Ensure transparent governance by multi-stakeholder group
Become recognized as meaningful by patients, providers, payers, and other stakeholders

MS, multiple sclerosis; MS PATHS, Multiple Sclerosis Partners Advancing Technology and Health Solutions; MSPT, Multiple Sclerosis Performance Test.

New York University, and Biogen began the planning process to best design the tools, systems, and governance needed for an LHS in MS.

Methods for standardized clinical and imaging data collection that do not increase the burden on providers or generate significant incremental cost were an important aspect of the planning process. Technology was developed to allow patient self-administered clinical assessment, resulting in standardized, high-quality clinical data. Technician-based testing—specifically, Multiple Sclerosis Functional Composite testing—was adapted to a series of patient self-administered iPad-based tests to provide quantitative data related to processing speed, low-contrast visual acuity, manual dexterity, and walking speed (11). This was done in order to facilitate the neuroperformance testing for every patient with MS, even in a busy clinical practice (12–14). The iPad-based clinical assessment tool, called the Multiple Sclerosis Performance Test (MSPT), also enabled the collection of a structured patient history.

Because the clinical assessment was patient self-administered, there are differences between the MSPT and the physician-derived measures used in clinical trials and traditional MS practice registries. Neurologist-determined relapses and Expanded Disability Status Scale were replaced by patient-reported relapse and Patient Determined Disease Steps. Prior studies support the validity of self-reported relapses (15, 16) and showed a strong correlation between Patient Determined Disease Steps and Expanded Disability Status Scale (17–19). The MSPT also enabled the collection of quality-of-life data. The Quality of Life in Neurological Disorders (Neuro-QoL) measure was selected as a standardized, well-validated patient-reported outcome instrument (20–22). The computer-adapted version of Neuro-QoL was incorporated into the MSPT to minimize administration time.

Two standardized magnetic resonance imaging (MRI) acquisition sequences were incorporated into routine MS imaging protocols to enable the reliable calculation of brain atrophy and lesions at the point of care. Through a collaboration with Siemens Healthineers, a software prototype is currently in development, with a focus on workflow integration and performance adequate for individual patient clinical decision-making.

To enable translational research, an MS PATHS research substudy was implemented to enable the collection of blood samples under a research protocol that could be linked to the standardized clinical and imaging data for future analyses.

Participating Healthcare Institutions

To be eligible for MS PATHS, the participating healthcare institutions had to have an MS center with an active census of $\geq$500 patients that routinely used functional measures and MRI in their clinical practice and a willingness to further standardize aspects of their clinical and radiological assessments. In addition, each participating healthcare institution had to have at least one Siemens 3T MRI scanner available for clinical use. Each participating center had to be willing to implement a centralized health information exchange architecture to transfer the data to a research database and obtain approval of the project protocol by the institutional review board or ethics committee, information technology (IT) security, and/or data privacy committee and agree to adhere to Good Clinical Practice and ethical principles as outlined in the Declaration of Helsinki. The participating healthcare institutions of each investigator receive financial compensation for data shared and biosamples collected as part of this program based on fair market value.

Patients

Patients with a confirmed diagnosis of MS, including clinically isolated syndrome, and the ability to understand the purpose and the risks of the project are eligible to enroll in MS PATHS. In contrast with a traditional prospective observational study, the sites in MS PATHS agree to adopt the outlined standard of care, and the patients provide authorization for the use of protected health information in accordance with national and local subject privacy regulations. Authorization format was determined by the local institutional review board or ethics committee and ranges from the use of a standard medical information privacy waiver (four institutions) to an oral consent (one institution) to a full informed consent (five institutions). The investigators and research coordinators are encouraged to invite all patients at each MS center to participate. At steady state, the network aims to have 80% of the MS patients at each participating MS center enrolled in MS PATHS.

Procedures

Upon enrollment, the patients are assigned a unique MS PATHS identification number that acts as the patient identifier in the LHS. This allows linkage of pseudonymized data from different sources for the same patient. The authorization form allows for prospective data sharing as well as sharing of data from 12 months before the date of consent.

The data elements collected routinely for patients in MS PATHS are listed in **Table 2**. Clinical data are collected using the MSPT. In addition, structured clinical data are shared from electronic medical records at each institution. Imaging data

TABLE 2 | Current data elements collected in the MS PATHS learning health system.

Patient demographic information (MSPT and EMR)
- Age (EMR)
- Gender (MSPT)
- Race (MSPT)
- Ethnicity (MSPT)
- Education (MSPT)
- Employment status (MSPT)
- Insurance coverage type (MSPT and EMR)
- Living situation (MSPT)
- Employment status (MSPT)
- Dominant hand (MSPT)

MS and other medical history (MSPT and EMR)
- MS subtype (MSPT)
- Age at first MS symptom onset (MSPT)
- Age at MS diagnosis (MSPT)
- Mobility aid use (MSPT)
- Smoking status (EMR)

Physical and laboratory assessments (EMR)
- Weight and height
- Body mass index
- Blood pressure
- Laboratory test values

Medications (MSPT and EMR)
- Patient self-reported use of MS disease-modifying therapy (MSPT)
- Medication list (EMR)

Patient-reported outcomes and tests (MSPT)
- Patient-reported relapses
- Patient Determined Disease Steps
- Neuro-QoL
  - Mental
    - Ability to participate in social roles and activities
    - Anxiety
    - Cognition
    - Depression
    - Emotional and behavioral dyscontrol
    - Positive affect and well-being
    - Satisfaction with social roles and activities
    - Stigma
  - Physical
    - Fatigue
    - Lower extremity function (mobility)
    - Sleep disturbance
    - Upper extremity function (fine motor, ADL)
- Neuroperformance testing
  - Walking Speed Test
  - Processing speed test
  - Manual dexterity test
  - Contrast sensitivity test

MRI-related data
- 3D T1 and 3D FLAIR MRI
- Radiologist report of number of new or enlarging T2 lesions (EMR)
- Radiologist report of number of enhancing T2 lesions (EMR)
- Quantitative brain volume metrics*
- Quantitative T2 lesion metrics*

3D, three-dimensional; ADL, activities of daily living; EMR, electronic medical record; FLAIR, fluid-attenuated inversion recovery; MRI, magnetic resonance imaging; MS, multiple sclerosis; MSPT, Multiple Sclerosis Performance Test; Neuro-QoL, Quality of Life in Neurological Disorders.
**Under development.*

TABLE 3 | Standardized Siemens 3T brain MRI sequence parameters for MS PATHS.

Parameter	3D FLAIR MS-Pie (SPACE)	3D T1 MS-Pie (MPRAGE)
Resolution (mm)	1 × 1 × 1	1 × 1 × 1
Field of view	256 × 256 × 176	256 × 256 × 176
Orientation	Sagittal	Sagittal
Total acquisition time (min:s)	6:27	5:12
Repetition time (ms)	5,000	2,300
Echo time (ms)	392	2.96
Inversion time (ms)	1,800	900

3D, three-dimensional; FLAIR, fluid-attenuated inversion recovery; MPRAGE, magnetization-prepared rapid gradient-echo imaging; MRI, magnetic resonance imaging; ms, milliseconds; MS PATHS, Multiple Sclerosis Partners Advancing Technology and Health Solutions.

include brain MRIs acquired using two standardized sequences (three-dimensional fluid-attenuated inversion recovery and three-dimensional T1 acquired on Siemens 3T scanners; **Table 3**), information from radiology reports, and quantitative measures of brain atrophy and lesion metrics derived from an image analysis software prototype.

Data collected during patient care visits can also be linked to substudies. Each substudy requires a separate protocol and informed consent to allow for research assessments or procedures and for the linkage of the substudy data with patient care data. An example is an ongoing biorepository substudy that collects a one-time blood sample for future genomic analyses (10 ml for adult patients and 6 ml for pediatric patients) and repeated blood samples for future biomarker analyses (33 ml for adult patients and 13.5 ml for pediatric patients) not more frequently than every 6 months. The clinical phenotyping information for any genetic or biomarker analyses will be derived from the routine clinical care data that are shared as part of MS PATHS.

Governance

The governance for MS PATHS requires a structure and a process that:

(1) Are fair, transparent, and compliant for all participating organizations;
(2) Assure confidence from all participating organizations;
(3) Foster collaboration;
(4) Reinforce the clinical and research integrity of participating healthcare institutions;
(5) Ensure that all participating organizations have sufficient freedom to operate; and
(6) Foster innovation, limit risk, and enable long-term success.

A steering committee was tasked with:

(1) Providing strategic and operational guidance;
(2) Setting the MS PATHS scientific strategy;
(3) Creating and overseeing data and sample access rules;
(4) Monitoring performance; and
(5) Providing other oversight activities as needed.

The steering committee consists of six representatives from participating healthcare institutions and one representative from Biogen. Three steering committee seats are reserved for investigators from the institutions that collaborated with Biogen on the initial planning process (Cleveland Clinic Foundation, Johns Hopkins University, and New York University), and one seat each is designated for an additional US healthcare institution, an EU healthcare institution, and a radiologist in MS PATHS.

The steering committee governs a set of data and sample access subcommittees responsible for approving requests for MS PATHS data and samples. The healthcare institutions and Biogen each have separate data and sample access committees. Biogen employees do not sit on the healthcare institution committees and *vice versa*. Separate subcommittees for Biogen and participating healthcare institutions were set up to ensure the independence of research led by the participating healthcare institutions. The healthcare institution and Biogen subcommittees operate under the same procedures, and all approved uses of the data or the samples are posted on the MS PATHS research website, which is accessible to Biogen and the participating healthcare institutions to ensure transparency and promote collaboration. In addition to approving data or sample requests, these subcommittees are also responsible for reviewing resulting presentations or publications to ensure alignment with the original request. Biogen, as the sponsor, has no role in writing or editing publications unless a Biogen employee is a co-author.

Standardization

Participating healthcare institutions have implemented the MSPT (11, 13, 14), an iPad-based medical assessment tool that quantifies major MS-associated motor, visual, and cognitive symptoms and quality-of-life outcomes. The MSPT incorporates a structured patient history (gathers the patient's relevant demographic and socioeconomic information, MS history, MS treatment information, and self-reported disability using the Patient Determined Disease Steps) (17–19), 12 subscales of the Neuro-QoL (20–22), and an electronic adaptation of the Multiple Sclerosis Functional Composite (23). The adapted Multiple Sclerosis Functional Composite includes a processing speed test that is similar to the Symbol Digit Modalities Test; a manual dexterity test, similar to the 9-Hole Peg Test; a contrast sensitivity test, similar to the Sloan low-contrast visual acuity test; and a 25-foot walking speed test, similar to the Timed 25-Foot Walk. The MSPT is administered during routine clinical visits, typically prior to meeting with the healthcare provider. Depending on the institution, the results are immediately available to the healthcare provider *via* the patient's electronic medical record or *via* a results screen on the MSPT. The processing speed test, manual dexterity test, contrast sensitivity test, and 25-foot walking speed test demonstrate reliability, validity, and sensitivity to MS outcomes (13, 14).

In MS PATHS, the participating healthcare institutions collaborate with Biogen and Siemens Healthineers to implement two highly standardized MRI acquisition sequences (a three-dimensional magnetization-prepared rapid gradient-echo imaging and three-dimensional fluid-attenuated inversion recovery) that are readily available product sequences and consistent with recent MS imaging guidelines (24). The participating healthcare institutions have also implemented standardized fields in the radiology report for assessment of new or enlarging T2 lesions and contrast-enhancing lesions (if applicable).

Health Information Exchange Architecture

MS PATHS is enabled by health IT that supports the secure transfer, processing, and harmonization of clinical data for research purposes. Similar to the hub-and-spoke model of data transfer in health information exchanges, clinical source systems such as the electronic medical record systems at participating healthcare institutions (the spokes) will send data through a series of intermediary systems before the data are passed through to the central MS PATHS research database (also known as the LHS).

Each participating institution is supported by a separate gateway that is responsible for applying consent logic to incoming data and then conducting any needed format transformations to enable ingestion by a central data broker. The two data brokers, one for the United States and one for the European Union, manage a patient registration and consent index as well as a de-identification tool that pseudonymizes data. Patient data other than consent and registration information are deleted from each broker after five business days.

Biogen has contracted with an IT vendor to act as a trusted third party to build and operate the MS PATHS gateways and data brokers. This IT vendor is responsible for protecting and processing identifiable patient data before they are pseudonymized and sent to the LHS.

In the United States, the vendor has entered into business associate agreements with each participating healthcare institution. Biogen does not have access to the data in either broker. In the European Union, each healthcare institution has contracted with an additional IT vendor to serve as the initial intermediary prior to the edge gateway. The EU IT vendor completes an initial pseudonymization of the data before they are transferred to an institution's gateway and subsequently to the EU broker. Once the data are pseudonymized in a broker, they are transferred to the LHS. The LHS is logically isolated from the brokers so that both Biogen and researchers from participating healthcare institutions do not have access to identifiable patient data.

In the LHS, data are harmonized using industry-accepted clinical terminology standards such as SNOMED, Logical Observation Identifiers Names and Codes, RxNorm, National Drug Code, and International Statistical Classification of Diseases and Related Health Problems. The LHS data are available to be requested for research purposes by any researcher at a participating healthcare institution or at Biogen.

Statistical Analysis

Descriptive analyses were used to describe MS PATHS patient characteristics at the time of a patient's initial MSPT assessment. Continuous variables were reported as mean (SD) and categorical

TABLE 4 | Patient demographic and clinical characteristics at initial assessment.

Characteristic*	Value
Mean (SD) age (years)†	47.0 (12.4)
Female, *n* (%)‡	10,712 (73.2)
Race/area of origin, *n* (%)‡	
United States—race	11,236 (76.7)
White	8,933 (79.5)
Black or African American	1,419 (12.6)
Asian	75 (0.7)
American Indian or Alaska Native	46 (0.4)
Native Hawaiian or other Pacific Islander	10 (0.1)
Multiple	290 (2.6)
Other/unknown	368 (3.3)
Choose not to report	95 (0.9)
European Union—area of origin	3,407 (23.3)
Western Europe	2,927 (85.9)
Eastern Europe	197 (5.8)
Asia	12 (0.4)
Multiple	64 (1.9)
Other/unknown	138 (4.1)
Choose not to report	69 (2.0)
Age at diagnosis (years)§	35.4 (11.2)
Age at first symptoms (years)¶	32.6 (11.4)
MS subtype, *n* (%)‡	
Relapsing remitting	8,708 (59.5)
Secondary progressive	2,504 (17.1)
Progressive relapsing	1,247 (8.5)
Primary progressive	1,100 (7.5)
Missing	1,084 (7.4)
Number of relapses in past 12 months, *n* (%)‡	
0	7,615 (52.0)
1	3,156 (21.6)
2	1,915 (13.1)
≥3	1,705 (11.6)
Missing	252 (1.7)
Baseline DMT use‡	
Dimethyl fumarate	1,966 (13.4)
Glatiramer acetate	1,761 (12.0)
Fingolimod	1,645 (11.2)
Interferon#	1,492 (10.2)
Natalizumab	1,384 (9.5)
Ocrelizumab	748 (5.1)
Teriflunomide	562 (3.8)
Rituximab	272 (1.9)
Alemtuzumab	230 (1.6)
Other	115 (0.8)
Not taking any medication/medication not listed	4,418 (30.2)
Missing	50 (0.3)
Neuro-QoL *T*-score**	
Mental	
Ability to participate in social roles	47.3 (8.0)
Anxiety	51.1 (9.4)
Cognitive functioning	46.2 (9.0)
Depression	47.3 (8.0)
Emotional behavioral dyscontrol††	50.6 (9.9)
Positive affect or well-being††	52.7 (7.2)
Satisfaction with social roles	47.0 (7.5)
Stigma	47.9 (8.5)
Physical	
Fatigue	49.4 (9.9)
Lower extremity function	46.7 (11.2)
Sleep	52.7 (10.2)
Upper extremity function	45.4 (9.6)

DMT, disease-modifying therapy; MS, multiple sclerosis; Neuro-QoL, Quality of Life in Neurological Disorders.

**Data are reported as mean (SD) or n (%) for continuous and categorical variables, respectively.*

†n = 14,484, ††n = 11,567, ‡n = 14,643, §n = 13,904, ¶n = 14,236.

#Includes interferon beta-1a, interferon beta-1b, interferon beta-other, and peginterferon beta-1a.

***Mean (SD) score reference value 50 (10); n = 11,827.*

variables as percentages. Between-group differences were assessed using *t* tests and chi-square (χ^2) tests, as appropriate.

To test whether MS PATHS is more diverse than typical phase 3 clinical trials in MS, the characteristics of patients with relapsing–remitting MS (RRMS) enrolled in MS PATHS were compared with patients with RRMS pooled from six phase 3 randomized controlled clinical trials (RCTs) sponsored by Biogen (25–29). Comparisons of patients from MS PATHS vs. the pooled RCTs were made using Wilcoxon rank-sum tests and Pearson χ^2 tests. Standardized mean or proportion differences (i.e., effect sizes) were also calculated. C statistics for membership (30) and predicted probability (i.e., propensity score) distributions were estimated using multivariable logistic regression models to assess overall baseline characteristics (i.e., case–mix) similarity. To assess the extent of overlap in the two populations (MS PATHS vs. RCTs), 1:1 propensity score matching (31) was performed based on a 5:1 greedy match algorithm (32). Comparisons between the matched sample characteristics were made using McNemar's test or Wilcoxon signed rank test. Effect sizes and C statistics for membership were also reported.

To assess heterogeneity in terms of assessment frequency, separate Kaplan–Meier plots were created for each center, describing the time (months) between assessments. Heterogeneity at the level of the healthcare institution was tested using log-rank tests. Separate analyses were conducted for MSPT and MRI assessments.

RESULTS

MS PATHS Patient Population

As of August 5, 2019, 16,568 patients from 10 participating institutions in the United States ($n = 7$) and the European Union ($n = 3$) agreed to share their clinical data, representing 71.4% of patient census seen in the MS clinics within the network. As of the

TABLE 5 | Neuroperformance scores at initial assessment.

Mean (SD) parameter	All	RRMS	SPMS	PRMS	PPMS	F test, *p* value
Processing speed test (number correct)	46.6 (13.1) $n = 13,250$	50.0 (12.2) $n = 8,059$	41.3 (11.8) $n = 2,188$	40.3 (13.1) $n = 1,075$	39.8 (12.6) $n = 966$	$F = 532.97$ $p < 0.0001$
Contrast sensitivity test (number correct)	34.2 (12.7) $n = 8,277$	36.3 (11.6) $n = 5,254$	29.9 (13.6) $n = 1,222$	30.8 (13.5) $n = 611$	29.6 (14.5) $n = 541$	$F = 140.74$ $p < 0.0001$
Manual dexterity test (seconds)	27.4 (6.8) $n = 11,829$	25.9 (5.9) $n = 7,505$	30.9 (7.4) $n = 1,834$	30.1 (7.6) $n = 880$	31.0 (7.7) $n = 758$	$F = 459.18$ $p < 0.0001$
Walking speed test (seconds)	7.5 (4.6) $n = 11,758$	6.6 (3.2) $n = 7,504$	9.7 (6.4) $n = 1,778$	8.8 (5.3) $n = 899$	10.1 (7.1) $n = 747$	$F = 362.83$ $p < 0.0001$

PPMS, primary progressive multiple sclerosis; PRMS, progressive relapsing multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis.

cutoff date for the data included in this manuscript, the number of withdrawals was 158 (0.95%) and ranged from 0.12 to 2.91% of participants across the sites.

Of 16,568 enrolled patients, 14,643 patients completed at least one MSPT assessment; the characteristics at the time of initial MSPT assessment for these patients are shown in **Table 4**. Mean (SD) age was 47.0 (12.4) years and the population was largely female [$n = 10,712$ (73.2%)] and predominantly white, although the absolute number of non-white participants is substantial. Mean (SD) Neuro-QoL T-scores ranged from 45.4 (9.6) to 52.7 (10.2).

At their initial MSPT assessment, 69.6% of 14,643 patients reported the use of a DMT. The most frequently reported DMTs were dimethyl fumarate, glatiramer acetate, and fingolimod. DMT use was highest in patients with RRMS [6,495 (74.6%)] compared with patients with progressive MS [1,662 (66.4%) secondary progressive, 540 (49.1%) primary progressive, and 806 (64.6%) progressive relapsing; $\chi^2 = 349.5$; $p < 0.0001$].

The neuroperformance scores at initial assessment are summarized in **Table 5**. Patients with RRMS performed better on neuroperformance testing compared with patients with progressive disease.

Assessment Completion Rates and Data Volume

The initial completion rates for the MSPT component modules ranged from 56.5% (8,277/14,643; contrast sensitivity test) to 100.0% (14,643/14,643; MyHealth module; **Table 6**). Missing data resulted from the coordinator disabling the module for patients unable or unwilling to complete the test or the patient canceling the test themselves. Longitudinal MSPT data were available for 72.7% (10,640/14,643) of patients (**Table 7**). The average patient contributed 15.6 person-months of follow-up (95% CI: 15.5–15.8); overall, 166,158 person-months of follow-up have been accumulated.

A total of 14,414 MRI studies were collected from 8,364 unique patients, including 3,822/8,364 (45.7%) patients with longitudinal MRI data (**Table 7**). Of the 14,414 MRI studies received, 281 (2.0%) were rejected for being incomplete or not acquired using standardized sequence parameters. Of 14,643 patients with at least one MSPT assessment, 7,622 (52.1%) had at least one standardized 3T MRI.

TABLE 6 | MSPT module completion rates at initial assessment.

Module	Assigned, *n**	Completed, *n* (%)	Patient declined or unable to complete, *n* (%)
Processing speed test	14,643	13,250 (90.5)	1,393 (9.5)
Contrast sensitivity test	14,643	8,277 (56.5)	6,366 (43.5)
Manual dexterity test	14,643	11,829 (80.8)	2,814 (19.2)
Walking speed test	14,643	12,152 (83.0)	2,491 (17.0)
Neuro-QoL†	14,643	11,827 (80.8)	2,816 (19.2)
MyHealth‡	14,643	14,643 (100.0)	

*MSPT, Multiple Sclerosis Performance Test; Neuro-QoL, Quality of Life in Neurological Disorders. *MSPT assessments taken on the same day are combined into a single record. †A computer-adaptive quality-of-life measure included with the MSPT. ‡A structured patient questionnaire that records demographics, health history, use of multiple sclerosis disease-modifying therapy, and multiple sclerosis status.*

A one-time genetic sample was collected from 6,320 patients. Other blood samples have been collected at a total of 10,223 biobanking visits from 6,581 unique patients, including 2,584/6,581 (39.3%) with a longitudinal sample collected (**Table 7**). The 10,223 biobanking visits represent 129,986 individual samples received in the central laboratory. A total of 265 (0.2%) samples were rejected after the initial quality control checks.

Heterogeneity Observed Across Sites

After completing their initial MSPT, 64% and 81% of patients in MS PATHS completed a follow-up MSPT within 12 and 24 months, respectively (**Figure 1A**). The median time to complete a follow-up MSPT was ∼7.4 months after the initial MSPT. The median time to complete a follow-up MSPT varied considerably among the participating healthcare institutions, ranging from 3 to 13 months (**Figure 1B**; $\chi^2 = 2,575$; $p < 0.0001$).

After completing their initial standardized 3T brain MRI, 30% and 58% of patients in MS PATHS completed a follow-up standardized 3T brain MRI within 12 and 24 months, respectively

TABLE 7 | MS PATHS data volume ($N = 16{,}568$).

Assessment	Total assessments	≥1, *n* (%)	≥2, *n* (%)	≥3, *n* (%)	≥4, *n* (%)
MSPT	41,187	14,643 (100)	10,640 (72.7)	7,038 (48.1)	4,332 (29.6)
Median (IQR) duration since first assessment (days)			448 (282–650)	553 (390–725)	609 (478–763)
Brain MRI	14,414	8,364 (100)	3,822 (45.7)	1,510 (18.1)	470 (5.6)
Median (IQR) duration since first assessment (days)			469 (350–715)	721 (565–834)	859 (721–1004)
Biobanking	10,223	6,581 (100)	2,584 (39.3)	836 (12.7)	196 (3.0)
Median (IQR) duration since first assessment (days)			364 (224–483)	546 (421–637)	658 (609–736)

IQR, interquartile range; MRI, magnetic resonance imaging; MS PATHS, Multiple Sclerosis Partners Advancing Technology and Health Solutions; MSPT, Multiple Sclerosis Performance Test.

(**Figure 2A**). The median time between the two standardized 3T brain MRIs was ∼18 months. The median time to complete a follow-up standardized 3T brain MRI varied considerably among the participating healthcare institutions, ranging from 12 to 24 months (**Figure 2B**; $n = 721$; $p < 0.0001$). In four institutions, half of the patients had not yet had a second standardized 3T brain MRI.

DMT use varied across the participating sites, in terms of both whether or not a patient was treated with a DMT ($\chi^2 = 163.3$; $p < 0.0001$) and which DMT was prescribed ($\chi^2 = 2{,}584.6$; $p < 0.0001$; **Table 8**).

Heterogeneity Relative to Phase 3 MS RCTs

The patients in MS PATHS were significantly older and had a longer disease duration than the patients from the pooled RCTs (**Table 9**). In addition, the proportion of patients with no relapses in the last 12 months was higher in MS PATHS (54.4%) than in the pooled RCTs (1.4%). The logistic regression models predicting membership in MS PATHS resulted in a C statistic of 0.91 vs. the pooled RCTs. A C statistic of 1.0 indicates no overlap; 0.91 indicates that RCT patients were substantially distinct from patients in MS PATHS. Propensity score 1:1 matching of the 8,708 patients with RRMS in MS PATHS and 6,574 patients with RRMS in the pooled RCTs yielded 1,922 patients from each sample that were able to be matched (**Table 9**).

Research Utilization of LHS Data

The governing subcommittee has approved 58 data use requests and one sample use request. Based on these requests, 78 conference abstracts and manuscripts have been published. Two National Institutes of Health grants have been funded.

DISCUSSION

The Institute of Medicine, a member of the US National Academies, recommended foundational elements for an LHS (10) as an approach to address recognized challenges, including the need for consistent quality and efficiency, in the US healthcare system. These challenges are also recognized by healthcare systems and regulatory bodies outside of the United States such as the European Medicines Agency (2, 4, 33–35). As the first LHS in MS, MS PATHS was designed to incorporate each of the foundational elements outlined in the introduction.

There were three initial observations from MS PATHS. The first relates to the characteristics of patients with MS. Although the patients in MS PATHS demonstrate demographic and disease characteristics typical of other large MS cohorts, the clinical characteristics from patients with RRMS in MS PATHS are partially non-overlapping with the patients enrolled in clinical trials (25–29), thus reflecting a broader population. The patients in MS PATHS exhibited a broader range of ages, disability levels, disease duration, and DMT use, presumably because MS PATHS aims to enroll all patients with a diagnosis of MS, including clinically isolated syndrome, with no additional inclusion or exclusion criteria (e.g., requiring a relapse in the past 12 months, as is typically required in pivotal RCTs). MS PATHS is more racially diverse than previously reported trials; white patients make up 79.5% of the US MS PATHS population in comparison with 93.7% of the oral DMT clinical trial study population (36). The minimal inclusion criteria and the robust enrollment rates suggest that studies using the MS PATHS population will generate data that will be more generalizable than data from clinical trials, in which enrollment is more selective. It is also likely that patient characteristics obtained from MS PATHS will be more representative of the broader MS population than data from registries where a smaller subset of patients from a clinical practice in one location is selected for inclusion in the cohort (37).

The second observation is the demonstrated feasibility of real-time quantitative patient phenotyping as part of clinical practice. As of August 5, 2019, 88.4% of patients who gave permission for their clinical data to be used for research have completed at least one self-administered neuroperformance assessment. Also, standardized MRI acquisition sequences were incorporated into clinical brain MRI protocols, with 98% of scans passing the quality control assessments.

The third observation relates to the variability in practice patterns observed across participating healthcare institutions. We observed a significant inter-institution variability in the rate of return for follow-up and the average interval between assessments captured in MS PATHS, indicating that there is no uniform standard for visit frequency in the network. Follow-up interval is important when determining outcomes because visit frequency may influence observed event frequency, depending on how the information is captured. For example, individuals

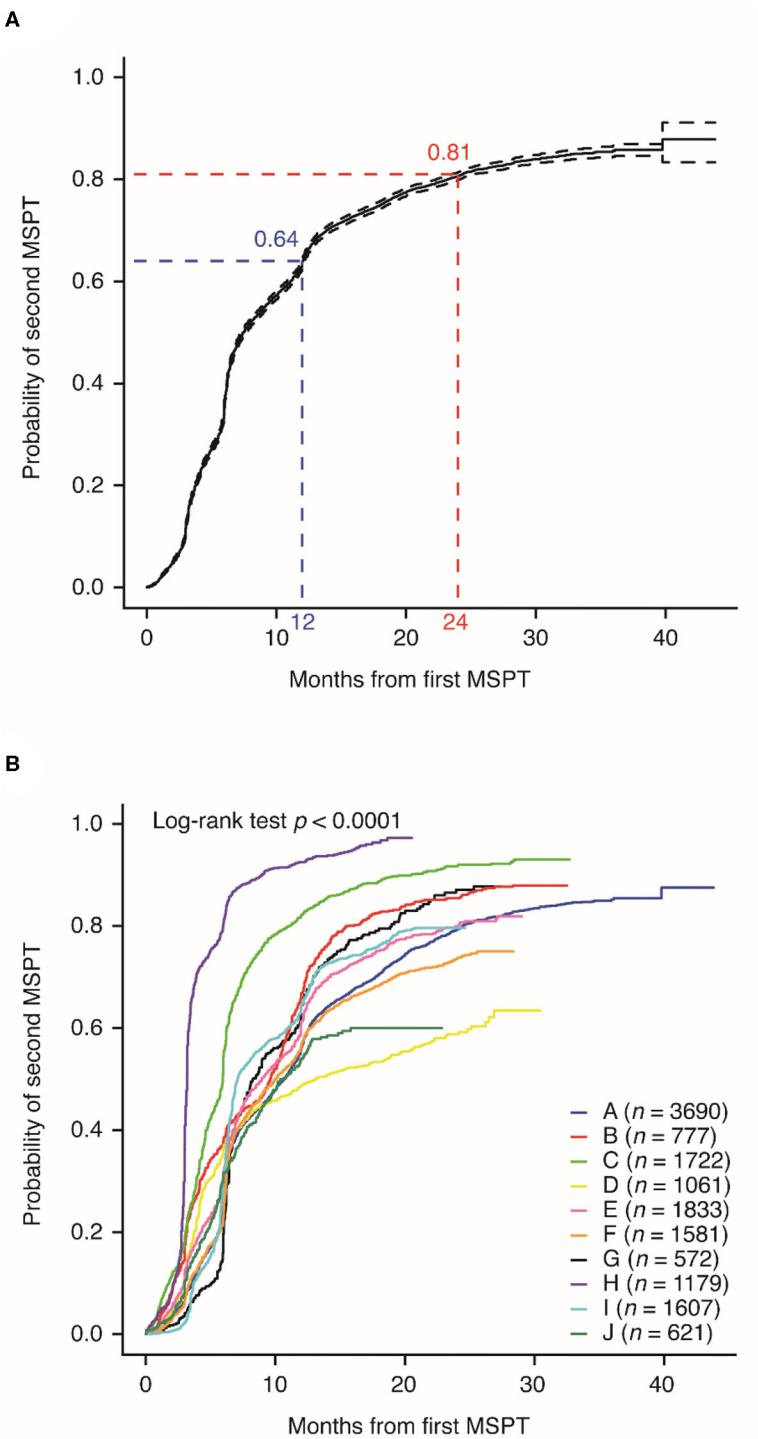

FIGURE 1 | Probability of completing a follow-up Multiple Sclerosis Performance Test (MSPT; as a function of months between the initial MSPT and completing the second MSPT), **(A)** overall and by **(B)** Multiple Sclerosis Partners Advancing Technology and Health Solutions center.

with MS may not always present to the physician during a relapse (38).

MS PATHS has experienced challenges and learnings during the initial implementation, including:

(1) Creating trust in an academic–industry collaboration: The initial collaborators were excited about the vision of MS PATHS; however, there were questions on how to build trust in a multi-party collaboration with a biopharmaceutical company. The

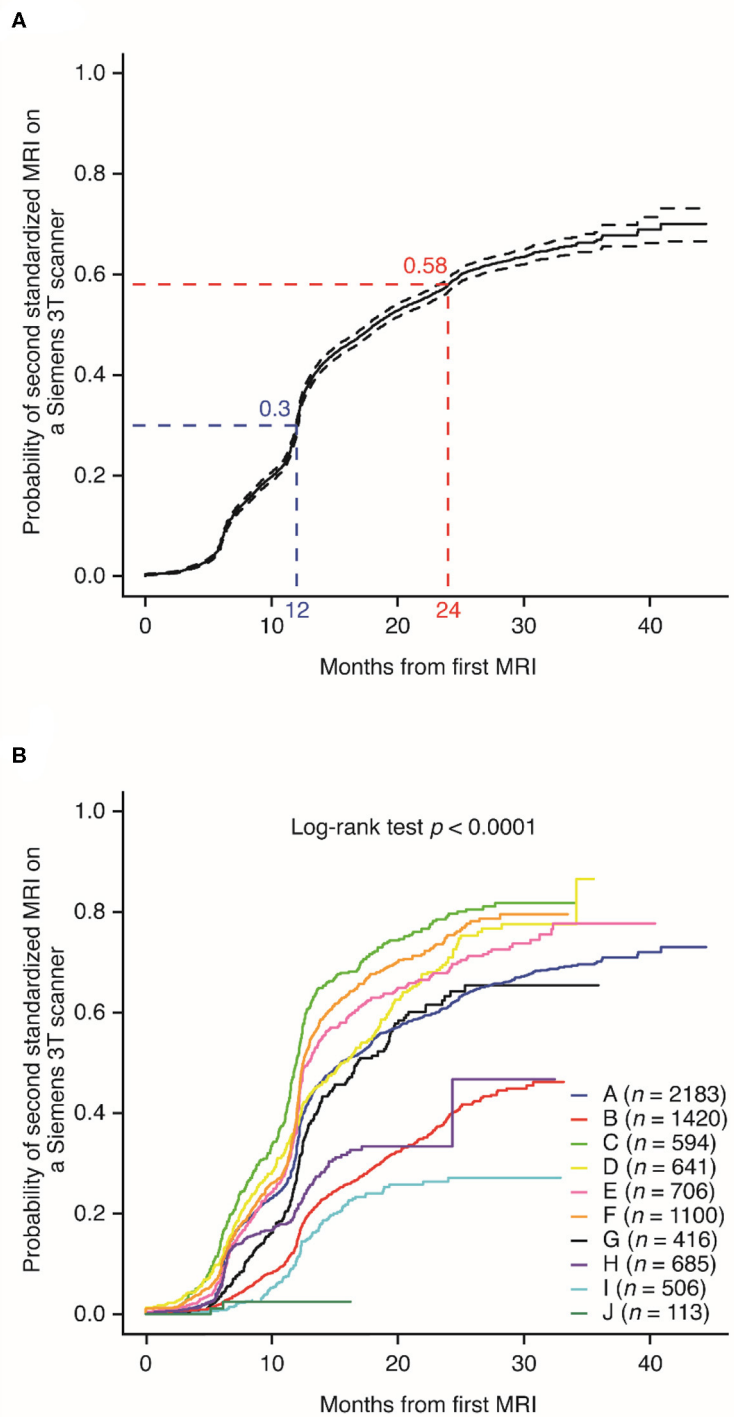

FIGURE 2 | Probability of completing a follow-up standardized magnetic resonance imaging on a Siemens 3T scanner, **(A)** overall and **(B)** by individual Multiple Sclerosis Partners Advancing Technology and Health Solutions center.

initial collaborators recognized that a transparent governance process would be key to engender trust among the participants and in the scientific community at large. All parties quickly aligned on a vision of using the LHS concept to generate evidence to improve outcomes for patients with MS as well as the guiding principles (**Table 1**). The governance model was then developed over the course of six all-day meetings to enable all parties to fulfill the shared vision and operate by the guiding principles.

TABLE 8 | Distribution of DMT use by participating healthcare institutions at initial assessment*.

DMT, *n* (%)	Overall (*n* = 14,643)	Institution									
		A (*n* = 1,581)	B (*n* = 1,061)	C (*n* = 572)	D (*n* = 1,722)	E (*n* = 3,690)	F (*n* = 777)	G (*n* = 1,833)	H (*n* = 1,607)	I (*n* = 621)	J (*n* = 1,179)
Alemtuzumab	230 (1.6)	12 (0.1)	3 (0.0)	4 (0.0)	103 (0.7)	19 (0.1)	14 (0.1)	4 (0.0)	28 (0.2)	0 (0.0)	43 (0.3)
Azathioprine	6 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.0)	2 (0.0)	2 (0.0)
Cyclophosphamide	2 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Daclizumab	37 (0.3)	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.0)	0 (0.0)	4 (0.0)	0 (0.0)	6 (0.0)	24 (0.2)
Dimethyl fumarate	1,966 (13.4)	152 (1.0)	159 (1.1)	67 (0.5)	179 (1.2)	641 (4.4)	104 (0.7)	317 (2.2)	115 (0.8)	104 (0.7)	128 (0.9)
Fingolimod	1,645 (11.2)	148 (1.0)	138 (0.9)	70 (0.5)	241 (1.6)	484 (3.3)	74 (0.5)	62 (0.4)	101 (0.7)	105 (0.7)	222 (1.5)
Glatiramer acetate	1,760 (12)	324 (2.2)	63 (0.4)	88 (0.6)	159 (1.1)	395 (2.7)	95 (0.6)	330 (2.3)	158 (1.1)	39 (0.3)	109 (0.7)
Immunoglobulin G	12 (0.1)	0 (0.0)	3 (0.0)	0 (0.0)	2 (0.0)	6 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Interferon beta-1a	1,088 (7.4)	171 (1.2)	50 (0.3)	44 (0.3)	67 (0.5)	295 (2.0)	41 (0.3)	129 (0.9)	225 (1.5)	31 (0.2)	35 (0.2)
Interferon beta-1b	245 (1.7)	12 (0.1)	10 (0.1)	11 (0.1)	13 (0.1)	13 (0.1)	9 (0.1)	14 (0.1)	130 (0.9)	16 (0.1)	17 (0.1)
Interferon beta-other	16 (0.1)	2 (0.0)	4 (0.0)	0 (0.0)	2 (0.0)	6 (0.0)	0 (0.0)	2 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Methotrexate	27 (0.2)	1 (0.0)	2 (0.0)	0 (0.0)	0 (0.0)	21 (0.1)	0 (0.0)	2 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Mitoxantrone	6 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)	2 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)	1 (0.0)
Mycophenolate mofetil	24 (0.2)	3 (0.0)	1 (0.0)	0 (0.0)	2 (0.0)	13 (0.1)	0 (0.0)	5 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Natalizumab	1,384 (9.5)	139 (0.9)	155 (1.1)	53 (0.4)	271 (1.9)	263 (1.8)	65 (0.4)	217 (1.5)	95 (0.6)	34 (0.2)	92 (0.6)
Ocrelizumab	748 (5.1)	27 (0.2)	60 (0.4)	64 (0.4)	140 (1.0)	173 (1.2)	21 (0.1)	108 (0.7)	23 (0.2)	27 (0.2)	105 (0.7)
Ofatumumab	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Peginterferon beta-1a	159 (1.1)	14 (0.1)	15 (0.1)	17 (0.1)	5 (0.0)	26 (0.2)	5 (0.0)	38 (0.3)	22 (0.2)	7 (0.0)	10 (0.1)
Rituximab	272 (1.9)	45 (0.3)	67 (0.5)	18 (0.1)	18 (0.1)	15 (0.1)	7 (0.0)	65 (0.4)	31 (0.2)	3 (0.0)	3 (0.0)
Teriflunomide	562 (3.8)	54 (0.4)	39 (0.3)	41 (0.3)	85 (0.6)	76 (0.5)	39 (0.3)	42 (0.3)	104 (0.7)	28 (0.2)	54 (0.4)
Other	1,077 (7.4)	139 (0.9)	74 (0.5)	20 (0.1)	110 (0.8)	298 (2.0)	68 (0.5)	98 (0.7)	103 (0.7)	58 (0.4)	109 (0.7)
None	3,341 (22.8)	337 (2.3)	214 (1.5)	75 (0.5)	317 (2.2)	922 (6.3)	234 (1.6)	395 (2.7)	465 (3.2)	159 (1.1)	223 (1.5)
Missing	35 (0.2)	0 (0.0)	2 (0.0)	0 (0.0)	5 (0.0)	20 (0.1)	0 (0.0)	1 (0.0)	5 (0.0)	0 (0.0)	2 (0.0)

DMT, disease-modifying therapy.

**Likelihood ratio (DMT × site) $\chi^2 = 2{,}584.6$; $p < 0.0001$.*

(2) Aligning on which data to collect and how to standardize data collection: Given the broad research goals of MS PATHS, the potential data to collect were vast. In the initial planning discussions, it became clear that standardizing and collecting all potential data would not fit into the clinical workflow. Data were prioritized in terms of time and utility. The goal was to keep MSPT administration no longer than 30 minutes for the average patient with MS, keep the brain MRI total scan time unchanged, and add no additional time to a clinician's clinical documentation. Any suggested patient-reported question or scale was weighed in terms of time to complete and its potential utility for clinical care and research. Implementing axial reconstruction of the standardized three-dimensional sequences allowed radiologists/neurologists to view scans as they normally would without the need for duplicative MRI acquisitions. Also, collaborating with Siemens Healthineers allowed the sequences to be optimized based on feedback from MS PATHS radiologists to enable broad adoption in the network.

(3) Implementation of common health IT platforms: Generating data in real time for clinical decision-making and providing pseudonymized data for research involved major technical challenges. We started with a basic design of a health information exchange platform and iterated after receiving feedback from key IT stakeholders at the founding institutions. Because IT architecture is different in each medical center, interfaces for the IT platforms need to be customized for each medical center to ensure compatibility and adherence to security requirements. The current implementation maintains consistent data handling and processing across the network but flexes to allow for variability in the interfaces and whether a push or pull model is optimal for each individual medical center. This type of model was aided by the increasing adoption of common healthcare data standards across healthcare in general.

(4) Ensuring compliance with US and EU data privacy regulations: MS PATHS was designed to be both HIPAA and GDPR compliant. In MS PATHS, patient data are only shared for research purposes, with patient consent. Trusted third parties serve as intermediaries to remove patient identifiers before the data are aggregated for research under appropriate contractual arrangements. Garnering acceptance and approval from a myriad of stakeholders at each institution is equally as important as a sound program design. MS PATHS has shown that with a

TABLE 9 | Demographic and clinical characteristics of patients with RRMS in MS PATHS and Biogen phase 3 RCTs (25–29).

Variable*	Unmatched population			Propensity score-matched population		
	MS PATHS	RCTs	Cohen's *d* value	MS PATHS	RCTs	Cohen's *d* value
N	8,708	6,574		1,922	1,922	
Age (years)	45.0 (12.2)	37.4 (8.9)	−0.71	40.7 (11.3)	40.3 (8.7)	−0.04
Male (%)	23.9	28.3	0.10	25.4	26.4	0.02
Body mass index (kg/m^2)	28.9 (7.0)	25.1 (5.4)	−0.60	27.9 (6.3)	27.8 (6.8)	−0.01
MS duration (years)	11.3 (9.0)	4.8 (5.0)	−0.90	7.2 (6.3)	7.1 (6.3)	−0.01
Manual dexterity test/9-Hole Peg Test (seconds)†	25.9 (5.9)	22.1 (6.1)	−0.63	25.1 (4.7)	25.3 (8.0)	0.03
25-foot walking speed test/Timed 25-Foot Walk (seconds)†	6.6 (3.2)	6.4 (4.5)	−0.04	6.5 (3.0)	6.5 (3.3)	0.01
Number of relapses in the past 12 months						
NA	0.8	4.6	0.24	1.9	2	0.01
0	54.4	1.4	−1.46	4.8	4.8	0
1	23.8	58.8	0.76	54.9	54.1	−0.02
2	12.6	29	0.41	26.5	26.7	0
≥3	8.4	6.1	−0.09	11.8	12.4	0.02

MS, multiple sclerosis; MS PATHS, Multiple Sclerosis Partners Advancing Technology and Health Solutions; NA, not applicable; RCT, randomized clinical trial; RRMS, relapsing-remitting multiple sclerosis.

**Data are reported as mean (SD) or n (%) for continuous and categorical variables, respectively. Cohen's d values represent standardized mean or proportion differences (i.e., effect sizes). An absolute value of % d >10 is considered as clinically meaningful.*

† The manual dexterity test and 25-foot walking speed test were administered in MS PATHS and the 9-Hole Peg Test and Timed 25-Foot Walk were administered in the RCTs.

sound program design, stakeholder engagement, and patient permission, data aggregation is feasible to conduct under both HIPAA and GDPR.

(5) Enabling efficient data sharing: Our chosen hub-and-spoke data sharing model simplified contractual relationships in MS PATHS. Each healthcare institution negotiated directly with Biogen rather than having to enter into a multi-lateral negotiation for the initial contract and any subsequent amendments. All stakeholders acknowledged the logistical benefits of this model. However, it required key clauses on the scope of data sharing, data permissions, and intellectual property to be uniform across all contracts and informed consent forms and for all parties to be comfortable that we could not accommodate one-off deviations if we were to maintain an effective hub-and-spoke model.

(6) Re-engineering of clinical workflows involved all aspects of clinic operations: One example of how MS clinics needed to change their operations was the incorporation of the MSPT into the clinical workflow. This necessitated designating space in the clinic as a MSPT testing area, training staff on the MSPT, introducing MS patients to a new aspect of their visit, and adjusting patient arrival times whether formally through a new appointment time or reminders to arrive 30 min before their scheduled visit with their healthcare provider. The workflow challenges differed somewhat for implementing the MSPT, implementing the standardized MRI protocol, and research workflows such as biobanking. Enthusiasm for the LHS tenets and the project sustained commitment from academic and industry project leaders, overcoming a myriad of challenges. The network investigators also committed to sharing best practices through conference calls, investigator meetings, and site visits. For example, an early MSPT implementation insight shared across the network was that patients generally have a better testing experience if they take the test without staff, a family member, or a caregiver by their side.

(7) Real-life experience highlighted gaps in original technical assumptions: Some design issues that have emerged and are being corrected include issues with MSPT functionality (e.g., lower-than-expected contrast sensitivity test completion rates) and issues with optimizing data collection methods for certain variables (e.g., comorbidities, medication start/stop dates). Among the advantages of an academic and industry partnership model are the real-time and continuous feedback, re-assessment, and refinement of data gathering and overall strategy that facilitate continuous improvement. One example of this feedback loop is the creation of a MS SmartForm by one of the MS PATHS institutions that is freely available in EPIC foundation to all EPIC users. This SmartForm will facilitate the standardization of key MS-related variables such as relapses and disease-modifying therapy start/stop dates to primarily aid clinical care, but with the secondary benefit of improving data quality for research. The US MS PATHS centers are currently in various stages of SmartForm implementation, while we are coordinating with the EU MS PATHS centers to harmonize as much as possible.

(8) Incorporating the voice of the patient: Patients have always been identified as a key stakeholder in MS PATHS. During the design phase, the investigators engaged a local patient advisory group, when available, on the MS PATHS concept. The MSPT was designed to facilitate the voice of the patient being incorporated into the clinical visit through the neuroperformance modules

and 12 domains of quality-of-life as assessed by the Neuro-QoL. Prior to the initial deployment of the MSPT in MS PATHS, qualitative feedback was obtained by the patients in an initial usability study (11). However, there is still more to be done to engage patients and complete the feedback loop as envisioned in a LHS (10). To start, the network is working to generate regular patient newsletters that provide updates on MS PATHS and summarize recent research presented at conferences or published in journals. Each MS center will provide these updates *via* their routine patient communication channels. We are also working on an updated publicly facing website that would also have this information.

(9) Moving from clinical implementation to clinical decision-making: Our efforts to date have been focused on the initial implementation and data collection as highlighted in this paper. The network is now shifting focus to evidence generation that will enable the data collected in MS PATHS to be used more routinely for clinical decision-making. Key next topics include understanding clinical cutoffs for the MSPT and MRI metrics, looking at practice heterogeneity across the network to identify best practices, and exploring feedback loops for investigators to more easily use the data for quality improvement.

Despite the promise of this research, there are limitations to be considered. Data missingness may be non-random. For example, patients with more disability may be less likely to have an MRI or complete the MSPT. The participating centers are referral centers and may not fully represent broader MS populations. For example, the rates of patients with progressive disease on a DMT may be higher than expected, and incorporation of the SmartForm data may provide additional insight. Still the MS PATHS population represents an improvement over the populations included in clinical trials as it is more racially and clinically diverse.

Another limitation is related to the restriction of standardized MRI studies to Siemens 3T scanners. This was intentional in order to remove scanner and manufacturer variability from the derived metrics as the initial step in delivering point-of-care MRI-based metrics to the clinician. As such, the time to follow-up MRI does not take into account the MRI exams acquired within each institution on non-Siemens 3T MRI scanners or using different (non-standardized) acquisition sequences or an MRI obtained outside the healthcare institution. Therefore, differences in MRI follow-up time between centers may reflect variations in the use of Siemens 3T scanners and variation in the percentage of patients who obtain MRI exams outside of the healthcare institution. A few participating centers image their patients with MS exclusively on Siemens 3T scanners, while others use a wide variety of scanner types across internal and external imaging facilities. Translation of the imaging methods to non-Siemens 3T scanners is planned.

The initial implementation of MS PATHS has been successful overall, although we are continuously optimizing aspects of our operations. We anticipate its value to grow with time as large-scale, longitudinal, and multidimensional quantitative data accumulate. These data will potentially drive new insights and aid in the development and the validation of new technologies. In particular, incorporating point-of-care quantitative MRI-based metrics in clinical practice has the potential to transform precision medicine to the same degree that MRI-based metrics have advanced clinical trials.

Another important direction for future work in MS PATHS is defining individual patient outcomes using quantitative standardized data. As MS PATHS data accumulate, it may be possible to define complete MS disease control or actionable change based on quantitative monitoring. Further, in the future, decision support based on advanced analytic methods could help neurologists care for individuals with MS in the context of a large number of DMTs and other therapeutic choices. Data accumulated in MS PATHS could support the development of predictive models and decision support systems.

The LHS concept, exemplified by MS PATHS, could accelerate translational research in MS as evidenced by the number of active proposals and grant approvals. Tens of thousands of patients may be required to unravel the biological basis for MS heterogeneity and develop personalized medicine based on individual patient characteristics. Using quantitative data derived from clinical, imaging, and laboratory assessments generated during patient care could drastically reduce the cost of, and thus make feasible, such translational research studies.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because MS PATHS is an ongoing study. Requests to access the datasets should be directed to datasharing@biogen.com.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics committees or institutional review boards at the following participating centers: Cleveland Clinic, Cleveland, OH, USA; Johns Hopkins University, Baltimore, MD, USA; New York University, New York, NY, USA; OhioHealth, Columbus, OH, USA; Washington University in St. Louis, St. Louis, MO, USA; University of Rochester Medical Center, Rochester, NY, USA; Cleveland Clinic Lou Ruvo Center for Brain Health, Las Vegas, NV, USA; University Hospital of Giessen and Marburg, Marburg, Germany; Vall d'Hebron University Hospital, Barcelona, Spain; and University Hospital Carl Gustav Carus, Dresden, German. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JW, CM, EF, and RR conceived and designed the data plan. CM and FP conducted the analyses. EM, RB, JW, and RR led the writing of the manuscript. RR had final responsibility for the decision to submit for publication. All authors provided critical feedback and helped shape the research, analysis, manuscript, had full access to the study data for interpretation and drafting of

the report, and contributed to the interpretation of the findings. Editorial support was provided to authors and funded by the study funder. All decisions relating to manuscript writing and content were made jointly by the authors.

FUNDING

Biogen provides funding for MS PATHS. As the sponsor of MS PATHS, Biogen facilitated the planning process and funded the development and ongoing operation/support of the MSPT and health information exchange architecture. Biogen entered into a research agreement with Siemens Healthineers to co-develop the MRI metrics prototype. Biogen also compensates participating healthcare institutions for data and samples contributed to MS PATHS at fair market value rates. Biogen serves as the hub for contracting and data sharing. All the participating healthcare institutions contracted with Biogen to receive consented patient data and allow Biogen to share the data with other researchers for uses consistent with the informed consent. As the data aggregator, Biogen curates the data and samples and then makes them available to researchers in the network who have an approved data or sample use proposal. To maintain the scientific integrity of the network, Biogen plays no role in adjudicating data and sample requests from academic collaborators or in conducting any scientific or editorial review of resultant publications. Biogen also does not permit its commercial employees to access the data.

ACKNOWLEDGMENTS

This study was funded by Biogen (Cambridge, MA, USA). Biogen provided funding for medical writing and editorial support in the development of this manuscript. Linda Wagner (Excel Scientific Solutions, Fairfield, CT, USA) wrote the first draft of the manuscript based on input from the authors, and Elizabeth Wassmer (Excel Scientific Solutions, Fairfield, CT, USA) copyedited and styled the manuscript per journal requirements. Biogen reviewed and provided feedback on the paper to the authors. The authors had full editorial control of the paper and provided their final approval of all content. The authors thank all of the patients who are participating in the MS PATHS initiative.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2020.00632/full#supplementary-material

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Conflict of Interest: The participating healthcare institution of each investigator receives financial compensation for data shared and biosamples collected as part of this program based on fair market value. EM reports research support from Biogen (MS PATHS and investigator-initiated studies) and Sanofi-Genzyme for investigator-initiated studies, serving as site principal investigator for a Sun Pharma study, free medication from Teva Neuroscience for use in a clinical trial, for which she is principal investigator, and royalties for editorial duties from UpToDate. RB reports consulting fees from Biogen, Genentech/Roche, Novartis, and Sanofi-Genzyme, research support from Biogen, and personal and institutional equity ownership related to the MSPT licensed to Biogen and Qr8 by Cleveland Clinic. JW, CM, EF, BK, FP, and RR are employees of and hold stock/stock options in Biogen. TB reports research support from Avid/Lilly and Roche, travel support from Biogen, and serving as clinical trial investigator for Avid/Lilly, Biogen, and Roche. CH reports speaking and consulting fees from Biogen, EMD Serono, Genentech, Genzyme, and Novartis, research support from Biogen, Genentech, and Patient-Centered Outcomes Research Institute, and research support to her institution, Cleveland Clinic, from Biogen. MH reports research support from Biogen, Chugai, National Institutes of Health (NeuroNEXT), Novartis, and Patient-Centered Outcomes Research Institute. II reports funding from Biogen in the form of a contract with her employer, Johns Hopkins University (JHU), to support effort on this project, serving as principal investigator on a research grant from Siemens paid to JHU for an unrelated project, and consultant fees from Alexion. SJ reports speaker fees from St. Jude Hospital, travel support from Siemens, grant support from Biogen for MS PATHS, and grant support from St. Jude Hospital. HK reports research support from Novartis and traveling and speaking/consulting fees and/or honoraria from Novartis, Biogen, Teva, IXICO, and Siemens. LK reports consulting fees from Biogen, Gerson Lehrman, Novartis, and Sanofi, grant support from Biogen, and receipt of royalties for the Fatigue Severity Scale licensed to various biopharmaceutical entities. YL declares no competing interests. XM reports speaker fees/travel expenses for scientific meetings or steering committees/advisory boards for clinical trials for Actelion, Biogen, Celgene, EXCEMED, Genzyme, Merck Serono, MS International Foundation, National MS Society, Novartis, Sanofi-Genzyme, Roche, and Teva. RN reports consulting fees and/or honoraria from Alexion, Alkermes, Biogen, Celgene, EMD Serono, Genentech, Genzyme, NervGen, Novartis, TG Therapeutics, and Third Rock Ventures. JN reports consulting/speaking honoraria from Biogen, EMD Serono, Genentech, Genzyme, and Novartis. AR serves on scientific advisory boards for Bayer, Biogen, Icometrix, Olea Medical, and SyntheticMR, is a consultant/speaker for Novartis, Roche, and Sanofi-Genzyme, and receives research support from Biogen. MS reports research funding for the conduct of MS PATHS from Biogen. BT reports advisory boards for Bayer, Biogen, CSL Behring, Genzyme, Grifols, Novartis, and UCB, speaker honoraria from Bayer, Biogen, CSL Behring, Genzyme, Grifols, Novartis, and Octapharma, consulting fees from Bayer, Biogen, CSL Behring, Genzyme, Grifols, Novartis, and UCB, and research support from Biogen and Novartis. MTin reports consulting/speaking honoraria from Almirall, Bayer Schering, Biogen, Genzyme, Merck Serono, Novartis, Roche, Sanofi, and Teva, grants from Biogen, Genzyme, and Novartis, and serving as co-editor of Multiple Sclerosis Journal – Experimental, Translational, and Clinical. MTiv reports funding from Biogen in the form of a contract with her employer, University of Rochester, to support efforts on MS PATHS. TZ reports speaker fees/travel expenses for scientific meetings or steering committees/advisory boards for clinical trials for Almirall, Bayer, Biogen, Celgene, Genzyme, Gilead, Merck Serono, Novartis, Roche, and Teva and grant support from BAT, Biogen, Genzyme, Merck Serono, Novartis, and Roche.

The handling editor declared a past co-authorship with AR.

frontiers in Neurology

ORIGINAL RESEARCH
published: 08 September 2020
doi: 10.3389/fneur.2020.00977

Cerebral Functional Manipulation of Repetitive Transcranial Magnetic Stimulation in Cognitive Impairment Patients After Stroke: An fMRI Study

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Objective: Recently, the area of repetitive transcranial magnetic stimulation (rTMS) targeting neurological rehabilitation has been advanced as a potential treatment for post-stroke cognitive impairment (PSCI). However, the underlying mechanisms remains to be elusived. This study aims to figure out cerebral functional manipulation of rTMS in patients with PSCI through using the resting-state functional magnetic resonance imaging (rs-fMRI).

Methods: Thirty patients with PSCI were recruited and randomly allocated into two groups: the rTMS intervention group and control group. The rTMS intervention group was given 20 min of 5 Hz rTMS (or control) over left dorsolateral prefrontal cortex (DLPFC) besides routine cognitive intervention training for 3 consecutive weeks, five times per week, on weekdays. Cognition performance was assessed by the Minimum Mental State Examination (MMSE) and Montreal cognitive assessment (MoCA). Neural activity and functional connectivity (FC) changes were acquired by rs-fMRI with fractional amplitude of low-frequency fluctuation (fALFF) and seed-based correlation analysis.

Results: Cognition improvements were observed both in rTMS intervention group and control group ($P < 0.01$), while the rTMS group got more significant improvent than control group ($P < 0.05$). To be specified, compared with the control group, the rTMS group got higher fALFF values in these brain regions including superior temporal gyrus, inferior frontal gyrus and parahippocampal gyrus, while lower fALFF values in middle temporal gyrus, middle frontal gyrus and fusiform gyrus. In addition, the rTMS group showed increased FC between LDPFC and toprecuneus, inferior temporal gyrus, middle and inferior frontal gyrus and marginal gyrus, while decreased FC between LDPFC and middle temporal gyrus and thalamus.

Conclusion: The increase and decrease of neural activity and FC in cognition-related regions detected by rs-fMRI are good indicators to clarify the underlining mechanisms of rTMS on PSCI.

Keywords: repetitive transcranial magnetic stimulation (rTMS), functional magnetic resonance imaging (fMRI), cognition impairment, brain activity, functional connectivity (FC), stroke

OPEN ACCESS

Edited by:
Simona Bonavita, University of Campania Luigi Vanvitelli, Italy

Reviewed by:
Carlo Cavaliere, Institute of Research and Medical Care (IRCCS) SDN, Italy
Giovanni Cirillo, Università degli Studi della Campania Luigi Vanvitelli, Italy

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Specialty section:
This article was submitted to Neurorehabilitation, a section of the journal Frontiers in Neurology

Received: *09 November 2019*
Accepted: *27 July 2020*
Published: *08 September 2020*

Citation:
Li Y, Luo H, Yu Q, Yin L, Li K, Li Y and Fu J (2020) Cerebral Functional Manipulation of Repetitive Transcranial Magnetic Stimulation in Cognitive Impairment Patients After Stroke: An fMRI Study. Front. Neurol. 11:977. doi: 10.3389/fneur.2020.00977

INTRODUCTION

Post-stroke cognitive impairment (PSCI) is a common complication after stroke troubling up to 75% of the survivors (1). Only half of the patients can achieve various degree of cognition recovery, while the others will still suffer cognitive impairment or even deteriorate to vascular dementia (2). PSCI inhibits the process to restore physical rehabilitations after stoke due to memory problems and poor judgment (3). Moreover, persistent cognitive deficit will result in the worse long-term outcomes such in the activities of daily living (ADL), community reintegration, and quality of life (QOL) even the physical functions (4–6). Therefore, early and effective treatment for PSCI has become one of the priorities of modern neurological rehabilitation.

Nowadays, the therapeutic strategies for PSCI are multitudinous ranging from pharmacological to non-pharmacological treatments, including some ongoing methods of computer-assisted cognitive training, physical exercise, and brain stimulations such as transcranial direct current stimulation (tDCS) and repetitive transcranial magnetic stimulation (rTMS). However, further studies need to be performed to confirm the validity and investigate the mechanisms of these stategies (7, 8). As a novel neuro-manipulated technique, rTMS has been widely used across a range of altered states including neurological and psychiatric conditions, especially popular in treating Alzheimer's disease (AD), mild cognitive impairment (MCI), depression, mental disease, and stroke with physical disorder, aphasia or dysphagia (9–15). The advantages of rTMS are non-invasively and painlessly modulating the cortical excitability (excite or inhibit) of both the stimulated region and some distant regions in the brain (16), and reorganizing functional connectivity among certain regions to ameliorate brain networks (17). However, to date, there are still limited evidences on the application of rTMS for PSCI with positive results (8, 18, 19) and very few studies investigating the underpinnings.

The changes come from rTMS in brain activity and connectivity can been detected through a variety of techniques such as transcranial magnetic stimulation (TMS), positron emission tomography (PET), near infrared spectroscopy (NIRS) (20), electro- and magnetoencephalography (EEG/MEG) (21), low-resolution electromagnetic tomography (eLORETA) (22), and finally functional magnetic resonance imaging (fMRI) (23). fMRI is rapidly becoming the most popular technique for its value of identifying the abnormalities of cortical activity and connectivity across almost every major neurological and psychiatric disease. Moreover, it promotes the detection of rTMS on neuro-manipulated mechanisms in these diseases (20). For instance, there have been a large body of studies reporting rTMS-induced beneficial effects on Alzheimer's disease, schizophrenia, and hemiplegia or aphasia after stroke, as well as investigating the neurophysiological underpinnings of these effects via the tool of fMRI (24–27). Despite its broadly use, a comprehensive understanding of the neurophysiological underpinnings of rTMS on the PSCI patients detected by fMRI is rarely reported.

Therefore, based on previous evidences that beneficial effects of rTMS on cognitive function recovery and the capability of fMRI to approach brain functional changes, we aimed to investigate the cognitive improvement of rTMS on stroke patients measured by fMRI.

So, in our study, 5 Hz rTMS (or control) were applied on the left dorsolateral prefrontal cortex (LDPFC) of stroke patients with cognition deficits. Resting state fMRI (rs-fMRI) was employed to investigate the neurophysiological evaluations, aiming to figure out the reorganization of relative cerebral function.

MATERIALS AND METHODS

Study Design

This is a prospective, single-center, randomized, double-blind, sham-controlled trial. It was approved by the ethics committee of Sichuan Academy of Medical Sciences & Sichuan Provincial People's Hospital, in Chengdu City, Sichuan Province, the People's Republic of China, and carried out at the inpatient department of Rehabilitation in this hospital between March 2016 and March 2018. Diagnoses were performed by board-certified and sophisticated physicians according to the cerebral apoplexy diagnostic criteria established by the 4th National Cerebrovascular Disease Conference. All participants (or their legal guardians) signed informed consent forms.

This study lasted three consecutive weeks, including a total of 15 sessions of rTMS (or sham) daily on weekdays. Group allocation was done according to the random numbers table to decide giving active or control stimulation on the participants. The grouping result was controlled by a secretary not directly involved in the research. Participants and the staff who held the assessments were fully blinded to the allocation status.

Participants

A total of thirty patients after hemorrhagic stroke with cognitive impairment were enrolled according to the inclusion and exclusion criteria as follows. The inclusion criteria were: (1) first-ever and hemorrhagic stroke with responsible lesions located in unilateral basal ganglia and/or corona radiate region confirmed by a brain computed tomography (CT) or magnetic resonance imaging (MRI); (2) stable vital signs, no deterioration of neurological symptoms; (3) $\leq$ 3 months from the accident; (4) aged between 50 and 75 years; (5) right-handed; (6) with cognitive disability: MMSE $<$ 24 (junior high school and above)/20 (primary school)/17 (illiteracy), which are cutoff values for cognitive impairment according to different education level (28); (7) without severe aphasia, visual or hearing impairment so as to be capable of fulfilling the study protocol. The exclusion criteria were: (1) non-first stroke; (2) prior history of cognitive impairment, epilepsy, or psychotic disorder; (3) cognitive dysfunction comes from other causes (e.g., alcohol addiction or drug abuse); (4) any comorbidity of serious medical conditions that could influence the study; (5) metal or electronic device implants (e.g., cardiac pacemaker, a cochlear implant, deep brain stimulator, aneurysm clip, ventriculoperitoneal shunt, or internal fixation devices); (6) cranial vault defects; (7) any non-compliance with the study protocol.

TABLE 1 | Demographic and Clinical characteristics.

Variable	rTMS	control	t/χ^2	*p*
N	15	15	–	–
Age (years)	65.47 ± 3.68	64.53 ± 4.72	0.604	0.551
Gender M/F (%)	7/8	9/6	0.536	0.464
Education (years)	9.20 ± 2.31	9.07 ± 2.63	0.148	0.884
Duration (days)	22.73 ± 8.05	19.13 ± 7.95	1.233	0.228
Affected hemisphere R/L (%)	5/10	6/9	0.144	0.705
Lesion localization: basal ganglia/basal ganglia and corona radiate region (%)	8/7	10/5	0.556	0.456

Mean± SD or frequency; t/χ^2, statistics of two sample independent t-test or Chi-square test; p, probability for the statistical analysis. rTMS, repetitive transcranial magnetic stimulation; N, number; M, male; F, female; R, right. L, left; SD, standard deviation.

Study Intervention

Group Allocation

The participants were randomly assigned to two groups: the rTMS group and control group with fifteen patients, respectively. The involved domains of cognition impairment including memory, attention, orientation, visuoconstructional skill, executive capability and abstraction ability. Demographic and clinical variables did not significantly differ between the two groups (see **Table 1**). Routine cognitive training was given to both groups. rTMS was applied to the rTMS group while control manipulation was given to control group, for three consecutive weeks, five times per week (except for weekends).

Routine Cognitive Training

Cognitive training covered several domains of cognition and performed as follows: (1) Memory training—including photo recognition, picture sequence recall, video content retelling, etc.; (2) Attention training—including visual tracking and computer game training; (3) Orientation training—tell the position of indoor furniture after visiting a simply decorated room; (4) Visual and spatial perception training—including puzzles, mazes, objects identifying; (5) Judging and reasoning ability training—computer game training, such as "spot the differences"; (6) Executive capability training—including origami, hand-making, knot solving, and setting up daily activities for patients to complete independently. Each patient was given certain domain or entire domains training according to the MMSE and Montreal cognitive assessment scale (MoCA) results. The training for all patients was delivered by a specific professional therapist and the cognitive tasks remained the same every day for each patient during the study, lasting 3 continuous weeks (30 min/time, 1 time/day and 5 days/week for total of 15 times in 3 weeks).

rTMS Procedure

Stimulation was delivered through the Magstim Super Rapid Transcranial Magnetic Stimulator (Magstim Company Ltd., Whitland, United Kingdom) equipped with a figure-eight air-cooled coil (70 mm mean diameter). The coil was positioned over the left DLPFC (29), which was positioned by using a standard EEG cap, based on the 10–20 International System (F3 region) (30). The coil was tangents to the surface of the skull, so as to produce a magnetic field that penetrates the skull into the brain. The motor threshold (MT) for each patient was determined prior to treatment, which corresponded to the minimum intensity able to stimulate the motor cortex and elicit a visible contraction of the first dorsal interosseus muscle of the unaffected upper extremity in at least 5 out of 10 attempts (31). Patient relaxedly slept in a semisupine position and kept the head unmoving during stimulation. The active stimulation session was set at a frequency of 5 Hz and 100% of the individual MT with a total of 50 trains, 40 pulses in each train, separated by 25 s inter-train interval. For the control stimulation, all parameters were the same as for the active treatment, except that the coil was located perpendicular to the surface of the skull to mimic the treatment procedure but bring no significant magnetic field into the brain. The stimulation was conducted by a specific qualified therapist and each patient received a total of 15 daily rTMS sessions, with the same machine and at the same daytime, over the course of three consecutive weeks (except for weekends). The transcranial magnetic stimulations were well-tolerated by all subjects.

Cognitive Assessment

All the participants were assessed for cognitive function at baseline and follow-up after 3 weeks' intervention via the MMSE and MoCA Beijing version, the widely used inspection tools for cognition status. The MMSE and MoCA scale cover multiple cognitive domains: MMSE assessed orientation, memory, delayed to recall, attention, force calculation, language and visual capacity, and the MOCA assessed naming, short-term memory, visuospatial abilities, executive function, abstraction, attention, concentration, language, and orientation (28, 32). Scores of MMSE range from 0 to 30 points, with higher scores indicating better cognitive function. For MoCA, cognitive impairment was defined as the score <26 (one point was added for subject with $\leq$12 years of education). The researcher performing the cognition assessments was blinded to the group allocation.

MRI Data Acquisition

The MRI examination was performed before and after intervention by a Siemens Tim Trio 3.0 T MRI scanner (Siemens Medical Systems, Erlangen, Germany) equipped with an 8-channel phased-array head coil. rs-fMRI images were acquired via a gradient- echo- planar imaging (EPI) sequence in the following parameters: repetition time (TR) = 3,060 ms, echo time (TE) = 30 ms, flip angle = 90°, slice thickness = 3 mm, slice gap = 1 mm, matrix size = 64 × 64, field of view (FOV) = 192 × 192 mm^2, and voxel size of 3 × 3 × 3 mm^3 (totally 160 timing slices on axial view). Additional high-resolution T1-weighted structural images of sagittal view were obtained by a magnetization prepared rapid acquisition gradient echo imaging (MP-RAGE) sequence using the following parameters: TR = 1,900 ms, TE = 2.52 ms, flip angle = 90°, slice thickness = 1.0 mm with no slice gap, matrix size =448 × 358, field of view (FOV) = 256 × 256 mm^2, and voxel size of 0.5 × 0.5 × 0.5 mm^3 (totally 176 images, taking 6 min and 5 s). During the

resting-state scan, participants were particularly instructed to keep their eyes closed, trying to "clear their mind" but not to fall asleep.

MRI Data Processing

The pre-processing of rs-fMRI acquisitions was carried out using Data Processing Assistant for Resting-State fMRI (DPARSF) (Version 2.3, http://rfmri.org/DPARSF_V2_3), running on MATLAB R2014a toolbox (33). The first five time series were removed from initial magnetization instability and participants' adaption to the scan condition, then the remaining 155 EPI images were corrected for differences in slice timing and for movement within and across the volumes. The average head motion should be <1 mm in x, y, z direction, and angular rotation should be within acceptable limits (<1°). Afterwards, the functional scans were coregistered to their corresponding T1-weighted anatomical image, and then spatially normalized into the standardized Montreal Neurological Institute (MNI, Montreal, Quebec, Canada) space, further resampled to 3 × 3 × 3 mm^3 of voxel size, and spatially smoothed using a Gaussian kernel of 6 mm full-width-at-half-maximum (FWHM). After that, the time series of each voxel was filtered (band pass 0.01–0.08 Hz) to remove the effects of very low-frequency drift and high-frequency noise. Finally, nuisance covariates including white matter and cerebrospinal fluid signal intensity were regressed out.

Fraction of amplitude of low-frequency fluctuations (fALFF) was calculated using the REST (version 1.8, http://www.restfmri.net/forum) software developed by Zou et al. (34) to measure the spontaneous neural activity. After pre-processing in DPARSF, a linear trend was removed, then the time series of each voxel were transformed into the frequency domain via Fast Fourier Transform (FFT) to get the power spectrum. Then the square roots of each frequency in the power spectrum were acquired and further the mean square root across a low-frequency range (0.01–0.08 Hz) was calculated, which was regarded as the ALFF index (35). fALFF refers to the ratio of the sum of the amplitudes at a low-frequency range (0.01–0.08 Hz) to the amplitudes of entire frequency range. At last, the acquired spatial fALFF maps were normalized with the fALFF value of each voxel divided by the whole-brain mean fALFF value and then called as "mfALFF" spatial maps.

The seed-based correlation analysis was used to detect the effect of local neural activity changes on whole brain functional connectivity (FC). The left DLPFC was defined as seed or region of interest (ROI) for FC analysis relying on the REST software. After filtering (band pass 0.01–0.08 Hz) and linear trend removed, the time series for each voxel within each seed were extracted in a sphere region (radius = 5 mm) and averaged over all voxels within the seed to acquire the mean time series of the seed region. Then Pearson's correlation analysis between the mean time series from in each seed region and that of every voxel in the whole brain was computed for a map of correlation coefficients, which were transformed to z-scores using the Fisher r-to-z transformation to improve normality and then called as z-FC maps.

Statistical Analysis

Clinical statistical analysis was performed using the SPSS Statistics 24.0 (IBM, NY, USA). Categorical variables were presented as absolute frequencies and percentages, whereas continuous variables were presented as means ± standard deviations (SDs). Differences between categorical variables were analyzed by Chi-square test while that between continuous variables were calculated by *t*-test. *P*-values were based on two-sided tests and compared to a significance level of <0.05.

Statistical analysis of fMRI data was conducted using Statistical Parametric Mapping package (SPM8, https://www.fil.ion.ucl.ac.uk/spm/), running on MATLAB. Two groups of both fALFF and FC maps after rTMS or control manipulation treatment were compared with a two-sample *t*-test, while changes post- and pre-rTMS (or control) treatment in each group were performed with a paired *t*-test. AlphaSim correction was adopted to conduct the multiple comparisons. The probability of false-positive detection was set to $P < 0.05$, and areas with a minimum cluster size of 82 contiguous active voxels were identified as significant regions.

In the rTMS group, Pearson's correlation was performed using multiple regression in the SPM8 to assess the relationship between the MoCA score and the seed-based FC alterations, with a significance level of <0.05.

RESULTS

Cognition Outcome

According to the cognitive assessment results, the details of involved cognitive domains were displayed as follows (**Table 2**). No differences were found between the rTMS group and the control group before intervention. There were significant improvements on cognition manifestation between pre-post scores for both groups. Moreover, the direct comparison of post differences between the two groups showed more significant improvement for the rTMS stimulation. See **Table 2** for details.

Lesion Location

Five out of the 15 patients in the rTMS group and six out of the 15 patients in the control group suffered right hemispheric lesion. So, the activation maps of those patients were flipped along the midsagittal plane to make the images of affected hemisphere corresponded to the left side for all patients.

rTMS Effects on fALFF

Compared to the control group, patients in rTMS group after intervention got higher fALFF values in these brain regions including the superior temporal gyrus (STG), inferior frontal gyrus (IFG), and parahippocampal gyrus, while lower fALFF values in the middle temporal gyrus (MTG), middle frontal gyrus (MFG), and fusiform gyrus ($P < 0.05$, with AlphaSim correction) (**Table 3** and **Figure 1A**).

rTMS Effects on Functional Connectivity

Compared with the control group, the rTMS group showed significantly increased FC between the LDPFC, toprecuneus, inferior temporal gyrus (ITG), MFG, IFG, and marginal gyrus,

TABLE 2 | Details of cognition tests.

Cognitive domains		rTMS group		Control group	
		Before	After	Before	After
Memory (*n*)		15	13	15	12
Attention (*n*)		12	10	11	9
Orientation (*n*)		10	7	12	10
Visuoconstructional skill (*n*)		15	14	15	15
Executive ability (*n*)		15	15	15	14
Abstraction ability (*n*)		15	14	14	14
Total score	MMSE	18.67 ± 3.90[a]	23.53 ± 3.23	19.13 ± 3.48	20.60 ± 3.16
	MoCA	20.47 ± 2.80[b]	24.40 ± 2.35	20.93 ± 3.04	21.80 ± 2.76
t-value/*p*		0.346/0.732[a]	0.438/0.665[b]	15.128/< 0.001[c]	15.849/< 0.001[d]
		6.813/< 0.001[e]	3.389/0.004[f]	2.516/0.018[g]	2.778/0.01[h]

n is the number of patients impaired; score values are mean± SEM. [a]Comparison of MMSE between the two groups before intervention; [b]comparison of MoCA between the two groups before intervention; [c]comparison between pre-post scores of MMSE for the rTMS group; [d]comparison between pre-post scores of MoCA for the rTMS group; [e]comparison between pre-post scores of MMSE for the control group; [f]comparison between pre-post scores of MoCA for the control group; [g]comparison of MMSE between the two groups after intervention; [h]comparison of MoCA between the two groups after intervention.

TABLE 3 | Significant differences in regional fALFF between the two groups after rTMS or control stimulation.

Brain region	Brodmann area	MNI coordinates			Clusters size	*t*-value
		x	y	z		
Regions showing increased fALFF in the rTMS group relative to the control group						
Superior temporal gyrus	22	39	24	−18	149	8.49
Inferior frontal gyrus	47	6	−57	−27	120	10.03
Parahippocampal gyrus	36	3	6	−21	138	13.78
Regions showing decreased fALFF in the rTMS group relative to the control group						
Middle temporal gyrus	21	−54	0	−27	136	−12.39
Middle frontal gyrus	11	45	36	−21	165	−6.65
Fusiform gyrus	36	−6	−27	3	139	−10.03

while decreased FC of the LDPFC was demonstrated in the MTG and thalamus (two-sample *t*-test, $P < 0.05$, AlphaSim correction, cluster size ≥ 82 voxels) (**Table 4** and **Figure 1B**).

Correlation Between fMRI and Cognition

In patients with rTMS stimulation, correlation analysis between FC values of regions with enhanced connectivity and cognitive manifestation after rTMS stimulation was calculated. The results showed that the DLPFC-precuneus/MFG/IFG/marginal gyrus FC values were positively correlated with the MoCA score ($r = -0.839/0.776/0.842/0.796$, $P < 0.01$, AlphaSim correction) (**Table 5**).

DISCUSSION

To the best of our knowledge, rTMS can modulate cortical excitability and may be a potential tool for cognition recovery in situations like AD, MCI, traumatic brain injury (TBI) and depression (10, 11, 36, 37), while was relatively less reported on stoke (8, 18). However, the neuroplasticity effects associated with beneficial cognitive effects from rTMS intervention still need to be thoroughly unraveled. Only few studies studied the effects of rTMS on cerebral functional reorganization in the poststroke motor dysfunction (26) or aphasia (27). Particularly, none of the previous studies have investigated the cognition recovery, as well as concerned rTMS-induced local neural activity changes and FC modulations in patients after hemorrhagic stroke. As the improvements in technology, a number of assessment methods can integrate well with rTMS to find the following neuroplasticity effects. Especially the neuroimaging tool-fMRI, which is able to provide rich information about brain activity and connectivity of various neural networks. It also could be an ideal device to reveal the underlying mechanisms of rTMS-induced neural reorganization in stroke rehabilitation (38).

To address the aforementioned limitations as mentioned above, in this study we conducted a randomized, sham-controlled clinical trial to investigate whether application of 5 Hz rTMS over the left DLPFC in stroke patients would improve cognitive

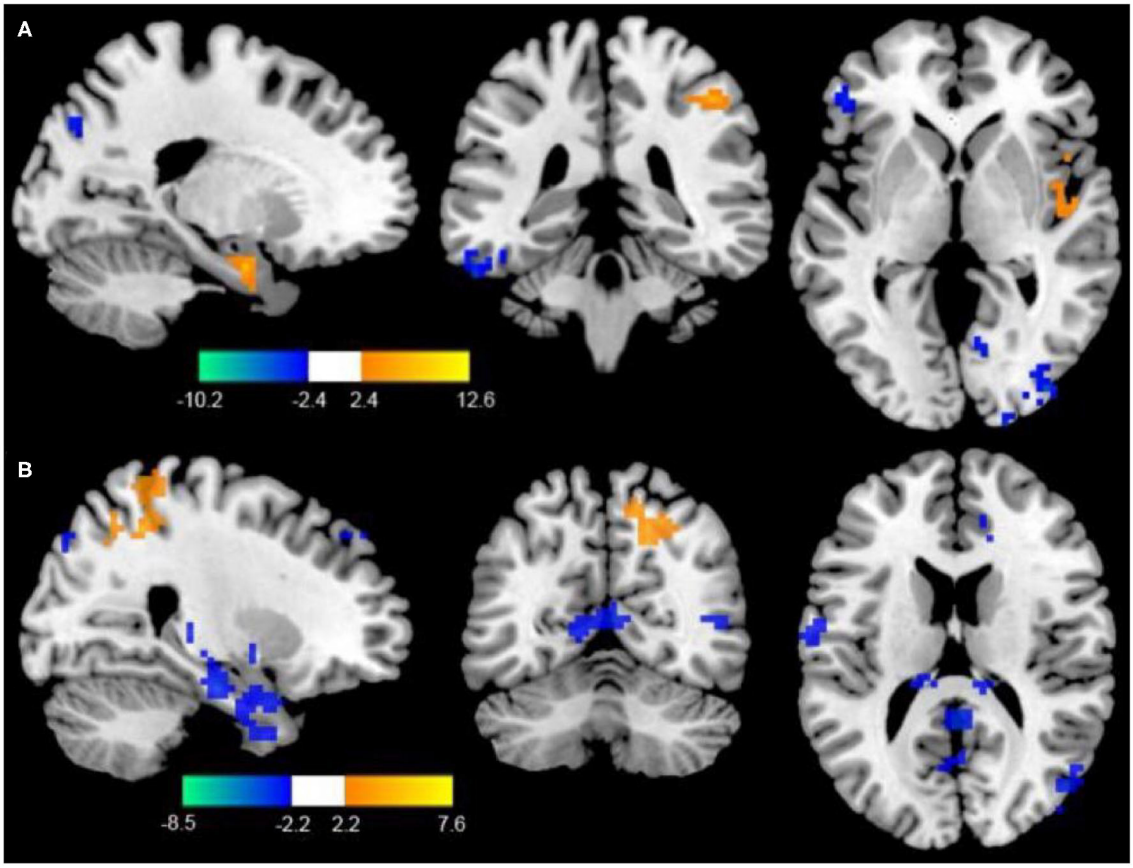

FIGURE 1 | (A) Differences of fALFF between the rTMS treatment group and the control group (two-sample *t*-test, $P < 0.05$, AlphaSim correction, cluster size $\geq$ 82 voxels). The yellow areas represent the regions which have increased fALFF, while the blue ones represent the regions which have decreased fALFF. **(B)** Differences of FC with the LDPFC between the rTMS treatment group and the control group (two-sample *t*-test, $P < 0.05$, AlphaSim correction, cluster size $\geq$ 85 voxels). The yellow areas represent the regions which have increased FC with the LDPFC, while the blue ones represent the regions which have decreased FC with the LDPFC.

manifestation, at the same time, explore whether rTMS could improve activity of cognitive related regions and modulate FC between the stimulated region with other areas in the cognition processing network. Notably, the results revealed significant cognitive improvements in patients with hemorrhagic stroke who received active rTMS intervention compared to control stimulation. Meanwhile, rs-fMRI demonstrated rTMS-induced neuroplasticity both in the stimulated regions and the other regions relate to functional network.

The Stimulation Site and Frequency of the rTMS Treatment

The default mode network (DMN), as a main resting state networks (RSNs) in the brain, plays a important role in cognition processing. Abnormalities of DMN activity are also involved in cognition deficits (39). DLPFC is a key node in the central executive network (CEN) (40), which is closely associated with mediating executive functions and particularly linked to the activity of the DMN (41). rTMS stimulating at the DLPFC is possibly to impact the entire DMN networks, particularly the medial prefrontal cortex (mPFC) (42), which is a key hub of the DMN. Moreover, previous studies have reported that high frequency rTMS to the left DLPFC or low frequency rTMS to right DLPFC could improve cognition functions in conditions including AD, MCI, bipolar depression and stroke at different degrees (8, 10, 22, 43). However, The evidences still not enough to show the best frequency and stimulation side for rTMS on treating these diseases, although high-frequency rTMS was prone to achieve better outcomes in some conditions like Alzheimer's disease and post-traumatic stress syndrome with less adverse effects (36, 44). In this regard, the current study chose left DLPFC as the targeted site with high frequency of 5 Hz.

There's two models of reorganization for non-invasive brain stimulation (NIBS) like rTMS in stroke recovery—interhemispheric competition and vicariation. Interhemispheric competition model supports that decreasing activity of the unaffected hemisphere with low frequency stimulation would be beneficial for stroke recovery by relieving the interhemispheric inhibition for the affected hemisphere. However, the vicariation model suggests that activity in the unaffected hemisphere serves as compensation for those functions lost by affected side. The

TABLE 4 | Significant differences in FC between the two groups after rTMS or sham stimulation.

Brain region	Brodmann area	MNI coordinates			Clusters size	*t*-value
		x	y	z		
Regions showing increased FC with the DLPFC in the rTMS group relative to the control group						
Precuneus	4	54	−66	12	150	7.21
Inferior temporal gyrus	20	36	3	−27	128	7.72
Middle frontal gyrus	11	18	51	30	147	4.76
Inferior frontal gyrus	47	48	0	33	180	3.79
Marginal gyrus	29	36	3	−27	134	7.29
Regions showing decreased FC with the DLPFC in the rTMS group relative to the control group						
Middle temporal gyrus	21	−60	−51	3	106	−7.31
Thalamus	26	−15	−27	12	125	−7.21

TABLE 5 | Significant differences in correlation between FC values and MoCA sore.

Brain region	Brodmann area	MNI coordinates			Clusters size	*R*	*p*
		x	y	z			
Precuneus	4	54	−66	12	150	0.839	<0.001
Inferior temporal gyrus	20	36	3	−27	128	−0.785	<0.001
Middle frontal gyrus	11	18	51	30	147	0.776	<0.001
Inferior frontal gyrus	47	48	0	33	180	0.842	<0.001
Marginal gyrus	29	36	3	−27	134	0.796	<0.001

two models lead to opposite conclusions about whether the given stimulation would be inhibitory or excitatory, ultimately affecting the therapeutic effect. By introducing a new parameter "structural reserve" describing the remaining functional neural output, the different judgements are unified by integrating the two models into a new model—the bimodal balance–recovery model, which proposes that the interhemispheric competition model can predict recovery better than vicariation model in patients with high functional reserve, otherwise the vicariation model is more useful in predicting recovery (45). Therefore, studying how to measure structural reserve, including clinical, anatomical and functional reserve in future researches, plays a key role in determining optimal stimulation site and frequency for an individual patient to improve efficacy of the treatment.

Improvements in Cognitive Functions After rTMS Treatment

In the present study, patients with cognitive impairment after hemorrhagic stroke were enrolled. Cognitive status were assessed by testing MMSE and MoCA scales. Our study showed that both the rTMS treatment and cognitive training can facilitate cognition recovery of stroke patients. Moreover, the combination of the two measures may amplify the profit of cognition enhancement. This result is also in line with several studies now available showing cognitive improvement after rTMS application for patients with stroke or Alzheimer's Disease (8, 46). Looking at the side effects of rTMS intervention, several patients experienced transient dizziness or headache in the rTMS group, and two patients complained light dizziness in the control group. These symptoms disappeared quickly without any specific interventions and no patient dropped-out of the study as to the adverse reactions. Therefore, rTMS assumed to be a safe, well-tolerated and efficacy intervention in treatment of stroke patients with cognition disorders. However, the preliminarily encouraging result needs larger controlled trials to further confirm the effectiveness of rTMS on PSCI.

Neural Activity and FC Changes After rTMS Treatment

Intrinsic activity of the brain is organized into networks which consist of many different nodes (47). Although the brain is constrained by the anatomical skeleton, the activities of each node and functional connectivity between any two nodes within these networks are dynamic (48). By means of spontaneous low-frequency oscillations in the blood oxygenation level-dependent (BOLD) signal, the resting-state functional magnetic resonance imaging (rs-fMRI) has provided a task-free approach which could eliminate some performance-related confoundings and provide a reliable measure of "baseline" brain activity and connectivity (49). Therefore, with the help of rs-fMRI, this study focused on characterizing how the cognitive-related networks dynamically change to unravel the mechanisms of cognition recovery after rTMS treatment.

The amplitude of low frequency fluctuations (ALFF) value is a sensitive index of resting state fMRI BOLD signal (0.01–0.08 or 0.10 Hz), reflecting the amplitude of spontaneous

neural activity in specific regions. While the fractional ALFF (fALFF) represents the ratio of low-frequency to the entire frequency range, which is superior to ALFF at suppressing noise components so as to enhance the sensitivity and accuracy of brain activity detection in resting state (48). Here, we found that the fALFF values of the rTMS group after intervention was significantly higher in the brain regions including the STG, IFG, and parahippocampal gyrus as compared to that of the sham group, while the values were lower in the MTG, MFG, and fusiform gyrus. The anterior STG is zoned as Wernicke region, functioning as the center of auditory information processing. The damage of Wernicke region may result in sensory aphasia which characterized by obvious auditory comprehension dysfunction and ultimately affect the cognition function for the poor words working memory. The increase of fALFF value in the STG may be related to the functional improvement of Wernicke area after rTMS treatment, accompanied by corresponding cognition improvement. The IFG is an important part of Broca region, and some studies have found that it is related to semantic acquisition and working memory (50). Increases of its fALFF value in this study again suggest that it plays an important role in cognitive function. The parahippocampal gyrus, as part of the medial temporal lobe (MTL) which is associated with memory encoding, storage, and retrieval, links the hippocampus, the retrosplenial cortex and the prefrontal cortex, plays a great part in episodic memory encoding, and retrieving (51). Therefore, the changes of the fALFF scores in these regions indicate that high-frequency rTMS over left DLPFC can facilitate corticospinal excitability, thus facilitating cognition recovery of stroke patients.

Functional connectivity (FC) analysis is extensively employed to evaluate correlations in activation among spatially-distinct brain regions for several functional neuroimaging methods, particularly fMRI either in a resting state or when processing external stimuli (38). The better correlation denotes more similarity of neural activities and stronger functional connectivity between regions (52). The rs-fMRI FC results in our study demonstrated a few discrepant brain areas between the two groups after the rTMS treatment, that is, the rTMS treatment group showed increased FC between the LDPFC and precuneus, MFG, IFG, ITG, and marginal gyrus, while decreased FC between the LDPFC and MTG and thalamus. Precuneus serves as a functional core within the default mode network. It simultaneously interacts with both the default-mode and frontoparietal networks to distinguish distinct cognitive states and plays a pivotal role in episodic and autobiographical memory (53), its latter part is also closely related to the conscious ephemeral memory (54). Frontal lobe is a highly evolved cerebral region, and richly interconnected with other cortical and subcortical structures through both short and large white matter pathways. It mainly works for integrating the afferent information from other brain regions and organizing efferent impulses timely, to ensure the overall synergy between the nervous system and psychosocial processes. It involves in a variety of higher functioning processing, including memory, abstract thinking, judgment, emotion, personality and impulsive behavior, etc (55–59). Hence, the enhancement of functional connections in frontal lobe with the LDPFC, such as MFG and IFG, has a strong connection with the improvement of cognitive function. The posterior MTG and the posterior fusiform gyrus are known to be involved in reading, and neuroanatomy has suggested that the region between the two is the posterior part of ITG which may play a core role in word cognition (60). Meanwhile, correlation analysis between FC values and cognitive manifestation after treatment in the rTMS treatment group showed that the DLPFC-precuneus/MFG/IFG/marginal gyrus FC values were positively correlated with the MoCA score. Therefore, the enhancement of functional connections in the above brain regions may be an important finding to understand the underlying mechanism of brain functional reorganization of high-frequency rTMS stimulation over the left LDPFC to facilitate cognitive function for stroke patients. As to the regions with decreased FC values, MTG plays a distinctive role in visual information processing, and its posterior part is closely connected with the language control area of the frontal parietal lobe so as to have more enhanced neural activity when performing language function (61). The thalamus is a subcortical relay station for various sensory and somatic motor signals, which plays an important role in advanced cognitive functions such as memory and emotion. After application of high frequency rTMS to the left LDPFC, the functional connections between LDPFC and the MTG and thalamus were significantly reduced, suggesting that this stimulation in our study may not have an obvious effect on improving the function of the MTG and thalamus.

Limitations of the Study

There are a number of methodological limitations to our study. First of all, we haven't assessed the immediate after-effects of rTMS on cognition-related regions by means of fMRI, since our fMRI acquisition was done at least 24 h after intervention. Therefore, our data doesn't represent short-term rTMS-induced neuroplastic effects. Furthermore, although comparisons of patient assessments at baseline showed no statistical differences, the interindividual variability in the neural substrate such as lesion site and volume, as well as given treatments like coil positioning may confound the results from the rTMS intervention to a certain extent. Further studies will focus on individual structural or functional mapping and stereotaxy to target and stimulate the precise brain regions by combining rTMS and fMRI. Finally, for patients with different degrees of cognition defect, we might failed to control all the patients keeping "clear their mind" but not falling asleep during the relative long scanning procedure, as such, it may cause another interindividual variability and influence the evaluation accuracy of the rTMS effect. Future studies should be conducted to ensure the consistency of rest-state while fMRI acquisition.

CONCLUSION

According to our study, high frequency stimulation of rTMS over left LDPFC can help to facilitate recovery of cognition in patients with hemorrhagic stroke. Our study also used the non-invasive rs-fMRI to observe the cerebral functional reorganization after the rTMS treatment and found increased or

decreased neural activity and FC in some significant cognition-related regions. From this perspective, rTMS may be a crucial and safe rehabilitation tool to enhance cognition rehabilitation for stroke patients, and the rs-fMRI is good method to provide unprecedented insights into both local and functional network levels of cerebral effects stimulated by rTMS.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Sichuan Academy of Medical Sciences & Sichuan Provincial People's Hospital ethics committee. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

QY and YaL designed the study and performed critical revision of the article. YaL, HL, KL, and JF performed the data collection. YaL and YiL analyzed the data. YaL wrote the article. All authors contributed to the article and approved the submitted version.

FUNDING

This study was supported by Foundation of Universal Application Projects of the Heath and Family Planning Commission of Sichuan Province (No.17PJ422).

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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ORIGINAL RESEARCH
published: 08 September 2020
doi: 10.3389/fneur.2020.00936

VSA-3000: A Quantitative Vibration Sensation Testing Device for Patients With Central Nervous System Injury

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Objective: To investigate the effect of using Vibration Sensory Analyzer-3000 (VSA-3000) in patients with impaired vibration sensation caused by central nervous system injury.

Design: Prospective observational study.

Setting: A university hospital for the research and clinical practice of rehabilitation.

Subjects: Sixty patients (30 stroke and 30 spinal cord injury) were recruited, aged between 20 and 71 years old, under stable medication.

Interventions: Not applicable.

Main Measure: VSA-3000 threshold test, tuning fork test and somatosensory evoked potential (SSEP) measurement.

Results: Test-retest reliability was determined based on data collected from 60 subjects, and the intraclass correlation coefficient (ICC) for vibration perception thresholds (VPTs) was in the "substantial" range. The kappa value between VSA-3000 and SSEP was 0.877, which was higher than that of tuning fork ($\kappa = 0.732$). VSA-3000 had good diagnostic accuracy with a sensitivity of 94.8%, specificity of 92.9%, and positive-predictive value of 93.8% and negative-predictive value of 94.0%, each value was higher than that of tuning fork. The area under the receiver operating characteristic curve (AUC) of VSA-3000 was 0.95 (95% CI: 0.91 to 0.98) and that of tuning fork was 0.89 (95% CI: 0.85 to 0.95), and there was a significant difference between the two values ($P = 0.0216$). The types of injury and age were the independent correlates of the VPTs.

Conclusion: The present study provides preliminary evidence that VSA-3000 is a non-invasive and convenient quantitative testing instrument with good diagnostic accuracy, and it may be useful as a screening tool for assessing impaired vibration sensation caused by central nerve injury.

Keywords: VSA-3000, vibration perception thresholds, quantitative sensory testing, central nervous system, stroke, spinal cord injury

OPEN ACCESS

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Specialty section:
This article was submitted to Neurorehabilitation, a section of the journal Frontiers in Neurology

Received: *30 January 2020*
Accepted: *20 July 2020*
Published: *08 September 2020*

Citation:
Gao M, Yun X and Zhang T (2020) VSA-3000: A Quantitative Vibration Sensation Testing Device for Patients With Central Nervous System Injury. Front. Neurol. 11:936. doi: 10.3389/fneur.2020.00936

INTRODUCTION

Symptoms of proprioceptive disorder are common in diseases of the central nervous system (CNS). Previous studies indicated that in 70 first stroke patients, 34–64% had impaired proprioception (1). About 50–80% of patients with spinal cord injury (SCI) have pressure ulcers caused by sensory (including proprioception) loss (2). In particular, diminished vibration sensation is an important

finding in the diagnosis of disorders affecting the dorsal column-medial lemniscus pathways in the CNS and may also be an early sign of CNS diseases (3).

Traditionally, a tuning fork is used for the evaluation of the vibration sense in patients with CNS diseases. This simple instrument has the advantage of being economical, portable, and quick for gross assessment of the sensory system (4), but unfortunately does not quantitatively provide the degree of dysfunction of vibration sense. It is of clinical importance that the vibration sense should be measured quantitatively and consistently. For this purpose, electrophysiology tests have been developed (5, 6), but they are invasive, time consuming, expensive, non-portable and requires a high standard of training to perform (4).

Recently vibration perception threshold (VPT) by quantitative sensory testing (QST) has been proposed as a method to assess the somatosensory pathways in clinical trials (7, 8). Multiple studies showed that VPT was a sensitive measure of peripheral neuropathy (9–17). The QST method for measuring VPTs has shown higher reliability than the tuning fork testing (7). Meanwhile it is painless and only requires brief training in comparison with electrophysiological testing (7, 18).

As one of QST computerized devices, the Vibration Sensory Analyzer VSA-3000 (Medoc) was designed to assess vibration. VPT assessed by VSA-3000 has been most commonly used in detecting peripheral neuropathy (9, 12–14, 19–23). Recent studies showed that QST using VSA-3000 (or other devices) was also a useful adjunct measurement with good reliability of detection thresholds in central nervous system diseases (6, 24–28). However a specific analysis of its diagnostic accuracy with VSA-3000, especially as diagnostic outcome measures in patients with stroke and SCI, has not been fully established.

Therefore, this study has two aims: (1) to estimate the diagnostic accuracy of the QST using VSA-3000 in evaluating VPT, in patients with CNS injury, against the reference standard of somatosensory evoked potential (SSEP) measurements, and (2) to assess whether the VSA-3000 device offers superior accuracy compared with other routine test (e.g., the tuning fork) for impaired vibration sensation caused by CNS diseases.

METHODS

Subjects

Individuals with stroke and SCI were recruited through advertisements posted at China Rehabilitation Research Center (CRRC) and Capital Medical University School of Rehabilitation Medicine, and by word of mouth (from May 2015 to March 2018). The study was approved by the Ethical Committee of CRRC.

Participants had to be: (a) age 18 years or older; (b) first-ever stroke (29) patients with unilateral sensory disturbance and with lesions in basal ganglia detected on radiological means, or patients with a thoracic or lumbar SCI; (c) medically stable conditions (patients' disease has not progressed within 1 week), ability to give informed consent and understand and cooperate with the testing. The exclusion criteria were presence of diabetes or other diseases involving neurologic impairments.

General Protocol

Subjects with stroke and SCI who met the inclusion criteria were scheduled for their first study visit. After informed consent was obtained, a neurological examination was conducted and a second visit was scheduled. During the second visit, three types of measurements (VSA-3000, tuning fork and SSEP) were conducted. Sixty participants (30 stroke and 30 SCI) in all completed an identical VSA-3000 test session ∼1 to 4 weeks later to provide data for the test-retest analysis portion of the present study.

Clinical Characteristics

Each participant's age, height, course of disease, and sex were recorded in the interview. For SCI patients, additional questions regarding the cause of injury were included [falls 14 (46.7%), violence 7 (23.3%), vehicle crashes 5 (16.7%), and others 4 (13.3%)]. For each participant with stroke, an experienced physician conducted a physical examination, to assess neurological status and to diagnose the type of the stroke according to the classification of cerebrovascular disorders of World Health Organization (29). For each participant with SCI, a physician with extensive SCI experience conducted a physical examination, including the American Spinal Injury Association (ASIA) standard examination (30), to assess neurological status and determine the severity (complete or incomplete) of injury.

The demographic characteristics of subjects were shown in **Table 1** and the distribution of neurological level of SCI participants was shown in **Figures 1**, **2**.

Tests

All the tests were performed by experienced physicians in a quiet room with an approximate temperature between 22 and 24°C. Subjects were tested in their own wheelchair to complete the tests of VSA-3000 and tuning fork, and lying prone relaxed for SSEP tests. Before testing, the examiner explained the procedures and several pilots were performed so that subjects could be familiar with the tests.

Figure 3 outlines the sequential tests.

TABLE 1 | Demographic characteristics of subjects ($n = 60$).

Age (yrs)	43.38 ± 12.98
Height (cm)	169.97 ± 6.49
Course of disease (d)	58.00 (33.25,96.50)
Sex	
Male	50 (83.3)
Female	10 (16.7)
Type	
SCI	
Incomplete	15 (25.0)
Complete	15 (25.0)
Stroke	
Hemorrhage	28 (46.7)
Infarction	2 (3.3)

Values are mean ± standard deviation, median (P25, P75) or n (%).

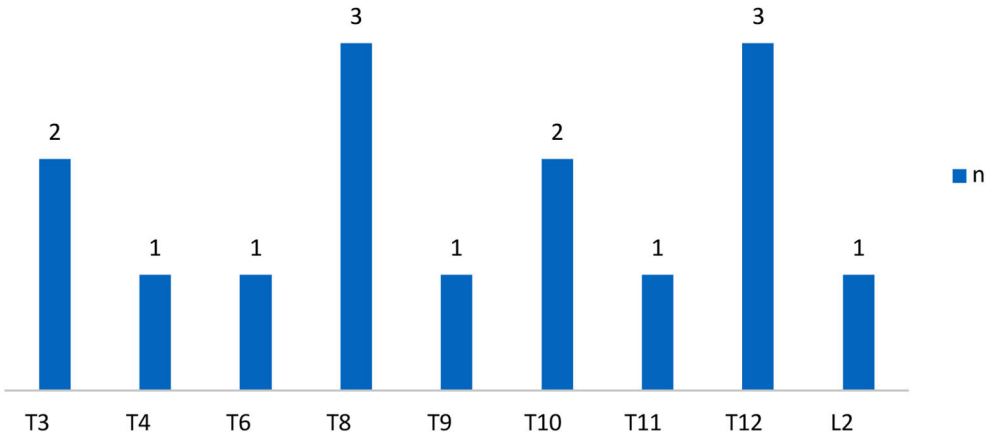

FIGURE 1 | Distribution of neurologic levels of injury in complete SCI patients. T, thoracic levels; L, lumbar levels; (30) n, numbers.

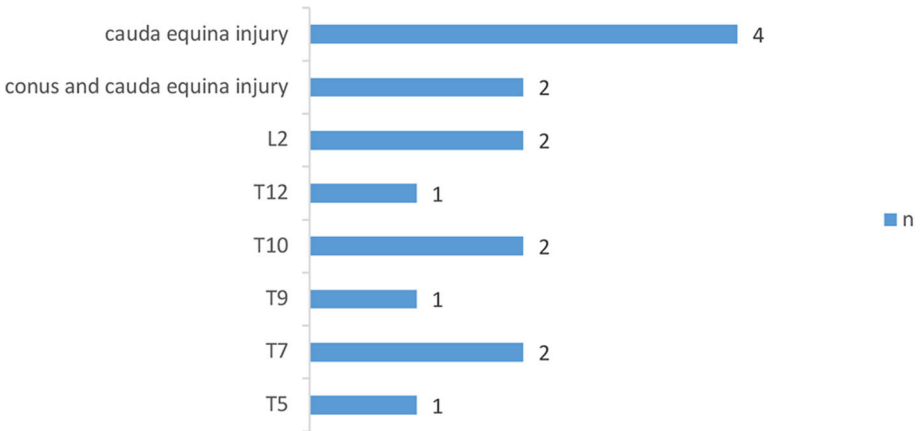

FIGURE 2 | Distribution of neurologic levels of injury in incomplete SCI patients. T, thoracic levels; L, lumbar levels; (30) n, numbers.

Quantitative Sensory Testing Using VSA-3000

Quantitative VPT was measured using the VSA-3000 vibratory sensory analyzer (Medoc Ltd., Israel) (**Figure 4**) following published protocols (31). The diameter of the stimulating probe was 1.2 cm and the vibratory stimulus was delivered at 100 Hz. The stimulating surface of the vibratory probe was placed on the hand (the palm side of the middle finger) and the foot (the plantar side of the great toe) (32).

The vibratory thresholds were measured by the method of limits (33). The device delivered the stimulus with increasing intensity starting from the baseline (0 μm) at a rate of 0.8 μm/s (lower limb) or a rate of 0.4 μm/s (upper limb) until the subject indicated that the stimulus was felt or until the maximum amplitude of 130 μm was reached. Subjects were asked to indicate by clicking the mouse as soon as they felt the vibratory sensation. The next trial started again from the baseline value, with the average of three successive trials (separated by 10 s each) (25) taken as the vibration perception threshold (VPT) for each site. To include data for analyses at sites where no sensation was evoked during testing, we recorded the maximum amplitude of the vibratory stimulus (cutoff value) (VPT=130 μm) (25). According to the standard of normal values specified by the VSA-3000 manufacturer, VPTs were divided into three groups (normal, decreased, and undetected) (**Table 2**).

Physical Examination Testing Using 128 Hz Tuning Fork

The vibratory sensation was tested with a 128-Hz tuning fork at the same sites as those in the VSA-3000 test. The examiner energized the tuning fork by fully opposing the two blades together where blades touched each other, rapidly released by slipping the fingers off the blade ends (34), and then immediately placed the base of the tuning fork on the test sites. The first measurements were taken at the palm side of the right middle finger of SCI subjects or at the palm side of the unaffected side middle finger of stroke subjects as a reference vibratory sensation (regarded as normal), then testing progressed to other sites, including the plantar side of bilateral great toes of all subjects and

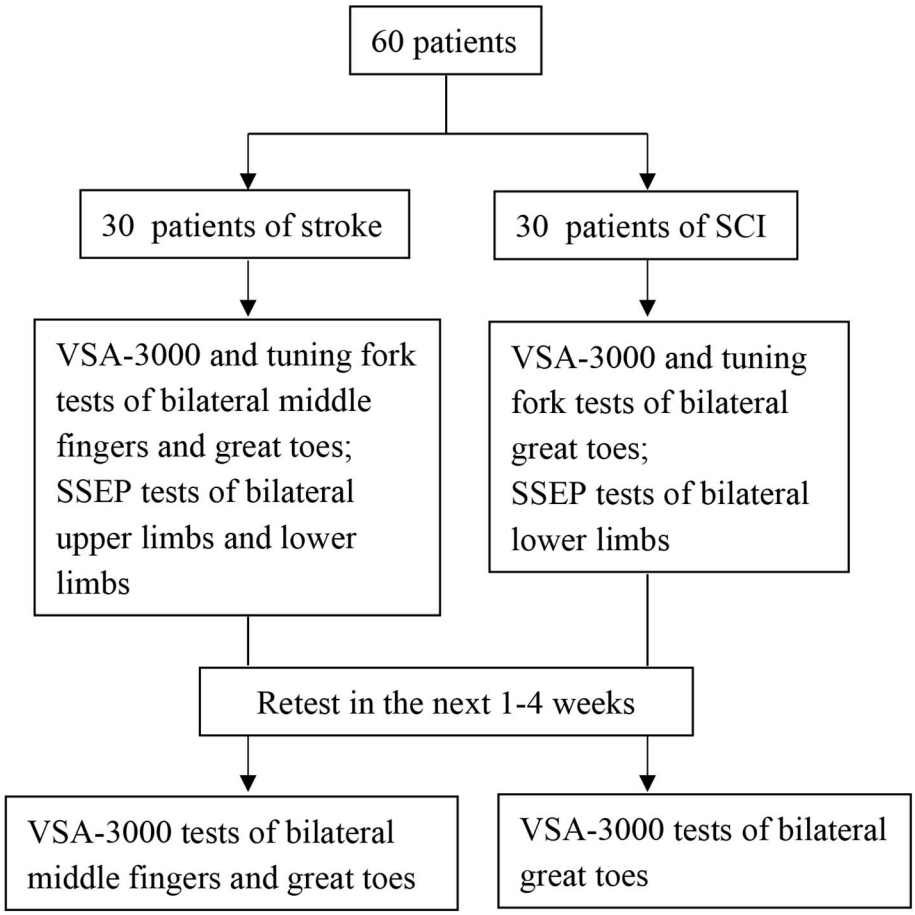

FIGURE 3 | Flow chart of the sequential tests.

the palm side of the affected side middle fingers of stroke subjects. In this manner, we could ask subjects to compare the quality of the sensation to the quality evoked at the reference hand. Appreciation of vibratory sensation at each site was separately scored on a 0-10 numerical rating scale scale (25, 35), with 0 = "undetected," 1–9 = "decreased," 10 = "normal."

Electrophysiology Testing Using Evoked Potential Instrument

Somatosensory evoked potential (SSEP) measurements were performed by a conventional EMG machine (Dantec Keypoint, Denmark). The tibial and median SSEP were elicited by electrical stimulation (square-wave stimulation of 0.2 ms at a frequency of 3 Hz) at the ankle or wrist with the cathodes placed 2 to 3 cm proximal to the anode (36). Stimulus intensity was adjusted to produce a clear muscular response (max 30 mA) in order to assess all sensory fibers (37).

According to the international nomenclature, in the waveforms of SSEP, positive peaks are represented by downward deflections and labeled P and negative peaks are represented by upward deflections and labeled N (38). The lower limb response elicited by electrical stimulation of the tibial nerve has a main positive peak with a latency of ∼40 ms labeled as P40, and the upper limb response elicited by electrical stimulation of the median nerve has a main negative peak with a latency of ∼20 ms labeled as N20.

For recording, scalp electrodes (0.5 cm silver plate electrodes) were applied at Cz′/Fz and C3′/C4′/Fz using the International 10/20 electrode system (39). The electrode impedance was maintained below 5 kΩ. The amplifier was set at 5 μv/division, frequency bandpass was set at 30–3,000 Hz. Three sets of 200 responses were averaged and superimposed to ensure consistency. The P40 and N20 latencies were recorded and used for statistical analysis.

STATISTICAL ANALYSIS

Test-retest reliability, a measure of the stability of a test when it is administered across time without changes in other variables, was evaluated separately for SCI and stroke subjects for VSA-3000 test by using intraclass correlation coefficients (ICCs) (one-way random effects model) (40). The assessment of the level of reliability was based on Shrout's recommendations: (41) an ICC of 0.21 to 0.4 indicate "slight," an ICC of 0.41 to 0.60 indicate

"fair," an ICC of 0.61 to 0.80 indicate "moderate," and an ICC of 0.81 to 1.00 indicate "substantial."

Kappa values and 95% confidence intervals (CI) were calculated to determine the degree of agreement between the data from VSA-3000 and tuning fork, VSA-3000 and SSEP, tuning fork and SSEP, respectively. Kappa values were used to test agreement between sets of results, which vary between 0 and 1 (0–0.50: slight to moderate agreement; 0.51–0.60: acceptable agreement; 0.61–0.80: substantial agreement; 0.81–1.00: almost perfect agreement) (42).

The sensitivity (ability of the test to correctly identify proprioception impairment), specificity (ability of the test to correctly identify proprioception spared), positive predictive value (proportion of positive test results that were from proprioception impaired patients), and negative predictive value (proportion of negative test results that were from proprioception spared patients) of VSA-3000 and tuning fork tests were calculated, using the results of SSEP tests as the criteria, and presented with 95% CI.

To compare the diagnostic accuracy of two types of tests against the reference standard of SSEP measurement, receiver operating characteristic (ROC) curve were constructed for each test (43), using the full range of possible thresholds per test. Areas under the receiver operating characteristic curve (AUC) are a measure of the performance of a test in predicting the outcome of interest. Generally, AUC values of 0.5 indicate that a test performs no better than chance, values between 0.70 and 0.79 indicate fair performance, values between 0.80 and 0.89 indicate good performance, and values ≥0.9 indicate excellent test performance (10). Statistical significance of the difference between the AUCs were tested with the method of DeLong et al. (44).

Stepwise multiple linear regression analysis (45) was used to examine the relationship between VPTs and age, height, gender, groups (stoke or SCI), types, and locations of injury of the patients. Types of injury were assessed by replacing types with dummy variables (cerebral hemorrhage, cerebral infarction, complete SCI, or incomplete SCI). Likewise, locations of injury were assessed by replacing locations with dummy variables (basal ganglia, SCI of thoracic levels, or SCI of lumbar levels and cauda equina injury and conus and cauda equina injury).

All analyses were performed using the version of SPSS 17.0. The significance level was set at $P < 0.05$.

FIGURE 4 | VSA-3000 (Medoc, Israel).

RESULTS

Data of VPTs and Tuning Fork

We described the VPTs measured with VSA-3000 (according to the age groups) and the tuning fork scores in **Table 3**. Four sites per one patient for 30 stroke patients and two sites per one patient for 30 SCI patients, therefore, in total 60 participants with 180 sites of data.

Test-Retest Reliability

Participants in the reliability of the study completed two identical VSA-3000 test sessions with ∼1 to 4 weeks between each session (mean interval = 15.7 days) (**Table 4**). The VPTs showed substantial reliability as the ICC is 0.91 (95% CI, 0.88∼0.93).

Consistency

With regard to the test results of tuning fork and VSA-3000, the kappa value was 0.731 (95% CI: 0.647 to 0.815, $P < 0.001$) (**Table 5**), indicating that the consistency of the two test results was not good enough.

When the consistency between the test results of VSA-3000 and SSEP was examined, the kappa value was 0.877 (95% CI:

TABLE 2 | Vibration perception thresholds (VPTs) of VSA-3000.

Age (yrs)		20–29	30–39	40–49	50–59	60–69	70–79
VPTs of middle finger (μm)	Normal	0–1.7	0–2	0–2.4	0–3	0–4	0–5.6
	Decreased	130≥VPT>1.7	130≥VPT>2	130≥VPT>2.4	130≥VPT>3	130≥VPT>4	130≥VPT>5.6
	Undetected	>130					
VPTs of great toe (μm)	Normal	0-8.2	0-10	0-14	0-22.8	0-43	0-90
	Decreased	130≥VPT>8.2	130≥VPT>10	130≥VPT>14	130≥VPT>22.8	130≥VPT>43	130≥VPT>90
	Undetected	>130					

TABLE 3 | VPTs measured with VSA-3000 and tuning fork scores.

	Age (yrs)	*n*	Middle finger		Great toe	
			Left	Right	Left	Right
VPTs	20–29	12	8.33 ± 8.02	3.2 ± 2.97	70 ± 62.87	69.36 ± 63.59
(μm)	30–39	12	102.73 ± 23.69	1.3 ± 0.46	85.83 ± 56.56	68.53 ± 64.23
	40–49	14	26.81 ± 43.94	24.1 ± 46.06	57.91 ± 56.75	52.67 ± 60.08
	50–59	17	37.27 ± 47.93	24.75 ± 47.22	66.26 ± 54.52	47.97 ± 48.68
	60–69	3	24.8 ± 31.68	65.9 ± 90.65	93.77 ± 62.76	88.5 ± 71.88
	71	2	5.8	130	15.2 ± 12.45	67.85 ± 87.89
Tuning fork	20–71	60	6.47 ± 3.85	10 (10, 10)	4 (0, 10)	9 (0, 10)

Values are mean ± standard deviation or median (P25, P75).

TABLE 4 | VPT results of test–retest.

Test	Patients	Middle finger		Great toe	
		Left	Right	Left	Right
First	Stroke ($n = 30$)	12.35 (2.30, 64.33)	2.55 (1.38, 19.05)	23.70 (15.25, 130.00)	11.90 (6.20, 64.55)
	SCI ($n = 30$)	NT	NT	130.00 (12.78, 130.00)	130.00 (10.58, 130.00)
Second	Stroke ($n = 30$)	32.02 ± 39.20	3.55 (1.80, 10.70)	52.63 ± 44.49	14.00 (6.43, 60.48)
	SCI ($n = 30$)	NT	NT	105.10 (12.20, 130.00)	125.35 (8.23, 130.00)

NT, not tested. Values are mean ± standard deviation or median (P25, P75).

TABLE 5 | Consistency for tuning fork and VSA-3000.

Tuning fork	VSA-3000			Total
	Normal	Decreased	Undetected	
10	76	6	2	84
1–9	7	28	11	46
0	0	5	45	50
Total	83	39	58	180

TABLE 6 | Results for 180 sites that were tested with VSA-3000 to distinguish between proprioception impaired and spared.

Results of VSA-3000*	SSEP results		Total
	Proprioception impaired	Proprioception spared	
Positive	91	6	97
Negative	5	78	83
Total	96	84	180

**A positive result indicates a VPT of VSA-3000 test is decreased or undetected, and a negative result indicates a VPT is normal.*

0.806 to 0.948, $P < 0.001$) (**Table 6**), indicating that there was nearly perfect agreement between the two test results.

Level of consistency between the test results of tuning fork and SSEP (kappa value, 0.732; 95% CI, 0.632 to 0.832; $P < 0.001$) (**Table 7**) was much lower than that between VSA-3000 and SSEP, which suggested that the test results of VSA-3000 were much closer to the SSEP test results than that of tuning fork.

TABLE 7 | Results for 180 sites that were tested with tuning fork to distinguish between proprioception impaired and spared.

Results of tuning fork*	SSEP results		Total
	Proprioception impaired	Proprioception spared	
Positive	84	12	96
Negative	12	72	84
Total	96	84	180

**A positive result indicates a score of tuning fork<10, and a negative result indicates a score of tuning fork = 10.*

Validity

The VSA-3000 test had a sensitivity (i.e., its ability to correctly detect proprioception impaired patients) of 94.8% (95% CI, 87.7 to 98.1%; **Table 6**) and a specificity (i.e., ability to correctly detect proprioception spared patients) of 92.9% (95% CI, 84.5 to 97.1%). The positive-predictive value of VSA-3000 (i.e., correctly identifying a proprioception impaired patient) was 93.8% (95% CI, 86.5 to 97.5%) and the negative-predictive value (i.e., correctly identifying a proprioception spared patient) was 94.0% (95% CI, 85.9 to 97.8%).

The tuning fork test had a sensitivity of 87.5% (95% CI, 78.8 to 93.1%) and a specificity of 85.7% (95% CI, 76.0 to 92.1%;

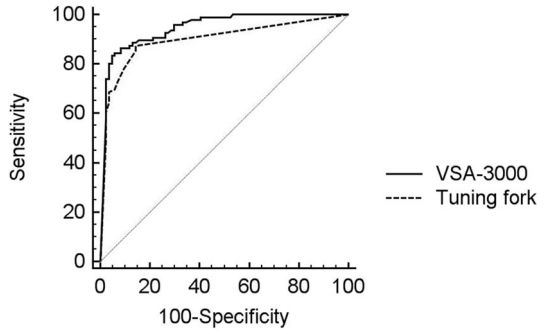

FIGURE 5 | ROC curve analysis was used to evaluate the diagnostic performance of VSA-3000 (black line) and tuning fork (dashed line) in detecting proprioception perception impairment against SSEP results using the evoked potential instrument. The gray line is the null value of the ROC curve.

Table 7), which were both lower than that of VSA-3000. The positive-predictive value was 87.5% (95% CI, 78.8 to 93.1%) and the negative-predictive value was 85.7% (95% CI, 76.0 to 92.1%), which were also lower than VSA-3000.

The diagnostic performance of the VSA-3000 and tuning fork (using continuous VPT outputs and tuning fork scores) in detecting proprioception perception impairment against the SSEP test results is given in the AUC using ROC curve analysis (**Figure 5**). The AUC for VSA-3000 is 0.95 (SE: 0.017, 95% CI: 0.91 to 0.98, $P < 0.001$) and the AUC for tuning fork is 0.89 (SE: 0.025, 95% CI: 0.85 to 0.95, $P < 0.001$). The diagnostic accuracy of VSA-3000 was significantly better than that of tuning fork ($P = 0.0216 < 0.05$).

Relationship Between VPTs and Demographic Characteristics

To investigate the relationship between VPTs and demographic characteristics of subjects, we performed a stepwise multiple regression analysis (n = 60) with VPTs as the dependent variables and age, height, gender, groups (stoke or SCI), types and locations of injury of the patients as independent variables. The types of injury (complete SCI vs. other types) and age were significantly related to VPTs ($R^2 = 0.389$, $P < 0.001$). None of the other factors significantly added to the model. Regression results are shown in **Table 8**.

DISCUSSION

The present study determined the use of VSA-3000 as potential diagnostic testing instrument for patients with CNS injury. Specifically, our primary aims were to determine the diagnostic accuracy of VSA-3000 against the reference standard of SSEP and to evaluate the superior accuracy compared with tuning fork in patients with CNS injury. Although the sample size was relatively small, this study provides preliminary support for the reliability and validity and the superior of this methodology in persons with stroke and SCI.

TABLE 8 | Multiple regression analyses predicting VPTs for participants with stroke and SCI.

Multiple regression analysis	β	*t*-value	*p*-value
Variables in model			
Types of injury (Complete SCI vs. Other types)	0.652	10.545	<0.001
Age	0.130	2.094	0.038
Variables not in model			
(Constant)	—	0.768	0.444
Height	0.049	0.766	0.444
Gender	−0.023	−0.392	0.695
Groups	0.004	0.048	0.962
Types of injury (Cerebral hemorrhage vs. Other types)	0.048	0.659	0.511
Types of injury (Cerebral infarction vs. Other types)	−0.072	−1.203	0.230
Locations of injury (SCI of thoracic levels vs. Other locations)	−0.049	−0.556	0.579
Locations of injury (SCI of lumbar levels and cauda equina injury and conus and cauda equina injury vs. Other locations)	0.029	0.483	0.630

Types of injury: cerebral hemorrhage, cerebral infarction, complete SCI, or incomplete SCI; Groups: stroke or SCI; Locations of injury: basal ganglia, SCI of thoracic levels, or SCI of lumbar levels and cauda equina injury and conus and cauda equina injury.

Reliability

In our sample of individuals with stroke and SCI, the test-retest reliability of threshold measures for vibratory detection showed substantial reliability (0.91). This result is consistent with studies in healthy, non-disabled subjects and in other patient populations (31, 46). A study by Felix and Widerström-Noga examined vibration thresholds across two test sessions in a sample of SCI patients with neuropathic pain and a sample of non-disabled control subjects, and the results showed that the ICCs were in the substantial range (0.86–0.90) (25). Two other studies have remarked on the stability of VPTs obtained in persons with SCI (24, 47). Krassioukov et al. found that the ICC in incomplete SCI patients for VPT was in the range 0.76–0.90 (24). A recent article aimed to determine the psychometric properties of the Graph-DCK Scale in people with SCI and neuropathic pain, involving detection of VPT in the test procedures, noted that ICCs for VPT were 0.83 and 0.85 for at-level assessment and below-level assessment, respectively (47). The previous studies results agree with our results, suggesting reasonable reliability of VPTs between sessions in patients with stroke and SCI.

Consistency

The high kappa value between VSA-3000 and SSEP reported in this study (0.877) indicated that there was excellent consistency between the two test results, which was higher than that between tuning fork and SSEP (0.732). Therefore, compared with tuning fork, the test results of VSA-3000 showed a higher degree of similarity to SSEP test results.

Some previous studies have focused on the relationships between VTPs and other measurements. Hayes et al.'s study found significant kappa values (denoted by κ) obtained from incomplete SCI patients for the association between VPT and light touch values for the right L4 ($\kappa = 0.25$) and left L4 ($\kappa = 0.29$) dermatomes and also a significant correlation between VPT and pinprick for the right L4 dermatome ($\kappa = 0.33$) (6). In addition, Santos et al. investigated the relationship between VPT and neuropathic signs of patients with type two diabetes, and found a clear trend toward progressively greater VPT in patients with mild and moderate/severe signs in contrast to patients with absent neuropathic signs (12).

Validity

In addition to the examination of reliability and consistency of VPTs in persons with stroke and SCI, a preliminary analysis of the validity of VSA-3000 test as diagnostic and outcome measures was also examined.

The present study used the sensitivity, specificity, positive- and negative-predictive values and ROC curves, as used by Martin et al. (10), to evaluate the utility of VPT to predict proprioception impairment.

The sensitivity and negative-predictive value of VPT obtained in our study compared favorably to Martin et al.'s study (sensitivities between 72 and 93% and negative-predictive values between 58 and 91%), however, the specificities (47–63%) and positive-predictive values (37–80%) of Martin et al.'s were lower than our study (10). The ROC curves demonstrate the clear tradeoff between sensitivity and specificity when VPT is used as a predictor of proprioception impairment. The areas under the ROC curve (AUC) suggest that VPT performance is excellent (0.95), which is higher than Martin et al.'s study of using VPT as a measure of distal symmetrical peripheral neuropathy in type 1 diabetes (0.71–0.83) (10). Two other studies have showed fairly good predictive performance of VPT. Santos et al. found the AUC of VPT for detection of diabetic peripheral neuropathy (DPN) in patients with type two diabetes was 0.71 (12), and Pritchard et al.'s study showed the AUC for diagnosis of 4-year incident DPN in type 1 diabetes was 0.74 (14).

The discrepancies between previous studies and our study may be attributed to applying in different type of diseases. The previous studies investigated VPT as a measure of peripheral neuropathy, and found VPT might provide important, clinically meaningful information about large nerve fiber dysfunction in diabetes (10). The present study used the VPT as a measure of proprioception impairment in central nervous system injury, in relation to electrophysiological testing (SSEP) as reference standard, as both measures are believed to reflect integrity of the dorsal columns (6).

In addition, the sensitivity, specificity, positive- and negative-predictive values and ROC curve of tuning fork were also evaluated, which were all lower than VPT. These results suggest that the degree of validity of tuning fork in persons with CNS diseases is similar to that seen in other patient populations. We noticed that Arshad and Alvi's study (48) showed that the tuning fork test, in patients with type 2 diabetes, had high specificity (93.70%), but low sensitivity (55.88%), the positive- and negative-predictive value were 70.37 and 88.81%, respectively, and the AUC for tuning fork is 0.75.

Relationship Between VPTs and Demographic Characteristics

Results from the multiple linear regression analysis in the present study suggest that the types of injury (complete SCI vs. other types) and age may significantly influence the VPTs, regardless of the height, gender, groups and locations of injury.

We show that the types of injury (complete SCI vs. other types) were the factor highly correlated with the VPTs. The possible reason for this result may be that most of the complete SCI patients had no sensation and therefore would artificially increase the correlations as the tests showed absent responses. Although Felix and Widerström-Noga's study showed the severity of injury (complete vs. incomplete) was not significantly related to Neuropathic Pain Symptom Inventory total intensity score (25), the participants of their study were SCI-related neuropathic pain and the relationship they investigated was between somatosensory thresholds and severity of neuropathic pain symptoms.

The current report indicates that vibratory thresholds changed linearly with age, which is not unexpected. Association between age and VPT has been previously shown in general populations (31, 49), and in diabetic patients (10, 12, 50). Many factors may contribute to decline of vibration sensitivity, such as age-related reduction in the receptor density, morphological modifications of the remaining receptors, and possible degeneration of corresponding peripheral nerves fibers (12).

Since height is highly correlated with latencies of cortical SSEPs (51–53), we include height in our methodology. Previous studies had reported that VPT, especially measured at the lower extremity, positively correlated with height (31, 54–60). However, we found no significant correlation between height and VPT in our patients with CNS injury. A possible cause for such interesting issue is that subject heights in our group were normally distributed with a standard deviation of only 6.49 cm; therefore, very few participants lay far from the mean to give strength to an analysis of height in this context (61). Although the lack of correlation should not be over interpreted in this relatively small sample, our findings are consistent with some studies in healthy subjects and in other patient populations that showed similar results (61–65).

All the results from this analysis should be viewed with a modest degree of caution, as the data available for this analysis were relatively small ($n = 60$). Although most other variables included in the regression analysis (height, gender, groups, and locations of injury) displayed non-significant relationships with the dependent variable, the lack of a mediating effect of these variables is inconclusive as a result of the low power.

Limitations and Future Research

The present study must be interpreted in the context of its potential limitations. We use latencies of SSEP, rather than amplitudes, as the reference criteria based on a consideration that "latencies seem to be more reliable in reflecting real damage,

whereas amplitudes vary inter-individually and depend more on the quality of the peripheral nerve stimulation" (37). However, some studies have been made to analyze both latencies and amplitudes for different research purposes (66, 67). The multiple linear regression analysis in the present study showed that the types of injury (complete SCI vs. other types) and age were the factor highly correlated with the VPTs, especially complete vs. incomplete spinal lesions. Studies in the past addressed this situation by either excluding complete SCI patients from the study or at least stratifying the population, with and without complete SCI correlations (6, 68). Therefore, the findings in this study need to be replicated in a larger study to further detail the reliability and validity of VSA-3000 test in people with stroke and SCI, and the amplitudes of SSEP will be incorporated in the evaluations and the SCI population will be stratified, with and without complete SCI correlations, in the future works.

CONCLUSION

Based on the results of the present study, VSA-3000 appears to provide a reliable and accurate assessment of impaired vibration sensation caused by central nerve injury. Use of VSA-3000 as a diagnostic and/or outcome measurement strategy may provide new motivations for its applications in the clinic and large-scale clinical trial researches.

CLINICAL MESSAGES

1. VSA-3000 has good diagnostic accuracy for assessing impaired vibration sensation caused by central nerve injury.
2. VSA-3000 is a non-invasive and convenient QST instrument that may provide a new method to quantitatively test vibration sense in clinic.

DATA AVAILABILITY STATEMENT

All datasets generated for this study are included in the article/**Supplementary Material**.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethical Committee of the China Rehabilitation Research Center. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

FUNDING

This research received funding from China Rehabilitation Research Center (No. 2014-Q5).

ACKNOWLEDGMENTS

We thank sincerely the reviewers for their insightful comments and helpful suggestions which have greatly improved the paper. We acknowledge all patients, physicians, and participants for their contributions in this study.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2020.00936/full#supplementary-material

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