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Biosensing in Multiple Sclerosis

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Abstract

Introduction: The goal of using wearable biosensors in multiple sclerosis (MS) is to provide outcome metrics with higher sensitivity to deficits and better inter-test and inter-rater reliability than standard neurological exam bedside maneuvers. A wearable biosensor not only has the potential to enhance physical exams, but also offers the promise of remote evaluations of the patient either at home or with local non-specialist providers.

Areas Covered: We performed a structured literature review on the use of wearable biosensors in studies of multiple sclerosis. This included accelerometers, gyroscopes, eye-trackers, grip sensors, multi-sensors and clinical trials.

Expert Commentary: Wearable sensors that are sensitive to change in function over time have great potential to serve as outcome metrics in clinical trials. Key features of generalizability are simplicity in the application of the device and delivery of data to the provider. Another important feature to establish is best sampling rate. Having too high of a sampling rate can lead to over interpretation of noisy data On the other hand, a low sampling rate can result in an insensitive test thus missing subtle changes of clinical interest. Of most importance is to establish metrics derived from wearable devices that provide meaningful data in longitudinal studies.
Keywords: accelerometer; biosensor; gyroscope; eye-tracking; multiple sclerosis; physical activity; review

1.0 Introduction:

Multiple Sclerosis (MS) is an immune-mediated chronic disease of the Central Nervous System (CNS). Inflammation and demyelination lead to neurological injury.[1-3] According to the World Health Organization, more than two million people suffer from MS making it one of the leading causes of disability in young adults.[4] Symptoms such as fatigue, pain, ataxia, and weakness lead to progressively decreasing levels of physical activity[5-7] This progressive loss of function can result in devastating effects on quality of life, as well as physical and emotional wellbeing.

There are critical unmet needs in current multiple sclerosis outcomes research. Current gold standard measurements of disability used in clinical trials, such as the expanded disability status scale (EDSS)[8], tend to be insensitive to change over the short term and are rater-dependent.[9-11] Infrequent physician exams provide only a partial snapshot of patient function. Wearable biosensors offer the opportunity to create more objective, less rater-dependent functional outcomes for MS patients with the potential for greater sensitivity to change over shorter time intervals than physical exam based metrics.[12]

The term biosensing has accumulated several definitions over the last few decades, but generally refers to converting biological signal into electrical signal. Biosensors are categorized as internal (e.g. biocatalyst or enzyme) or external (worn outside the body). For a digital biosensor, physical or electrical data are converted to digital data within the device. The most popular biosensors in commercial use include accelerometers and heart rate trackers. Gyroscopes, which

are used to provide stability but also provide a reference direction for detected movements, are also present in commonly used commercial devices.

Application of biosensors in the medical setting has been an intuitive progression in multiple specialties, but despite their overall attraction to providers and patients, rigor must still be applied in the scientific approach to their use. Currently, there is limited methodical agreement in using sensor-based outcomes.[13] Therefore, establishing the utility of a wearable device includes 1) rigorous data collection in diseased and healthy individuals 2) determining test re-test reliability of the measurements and 3) determining association with meaningful disease outcomes in cross-section and even more importantly over time in longitudinal studies.

We herein present a review of wearable biosensors used in the study of participants with multiple sclerosis to determine the applicability of these devices including inter-test reliability, correlations with current disability tools, and potential benefits of these sensors in MS. In addition, this review highlights where future research is needed.

2.0 Methods:

This review focused on biosensors used in MS participants. Literature review was performed using the PubMed database. Our search strategy utilized key words related to biosensing. A complete list of search terms is included in Table 1. This list includes synonyms of popular biosensors and activity measurements. Citations in articles found by the search were used to identify additional

publications of interest. We also then searched by authors that have commonly published with different biosensors. We searched clinicaltrails.gov for ongoing clinical trials utilizing biosensors in MS. The search included articles published through July 28th, 2017.

The inclusion criteria for this review included studies that used biosensor outputs as a primary or secondary outcome. Studies selected included evaluations of reliability of device data and comparisons with patient-reported survey data, or objectively measured disability in MS. Studies with a control group comparison and intervention studies were included if their experimental design included biometric outputs.

After reviewing each citation and eliminating any duplicates, the researchers read each paper and removed papers that did not meet the inclusion criteria stated above. An article was removed if it was a review or abstract. Afterwards, for each article methodology and results were reviewed. Information regarding each biosensor was compared to determine variation amongst biosensor use.

Table 1: Search Terms

Figure 1: Eligibility Determination for Review

3.0 Findings:

3.1 Study Description

Of the 3575 total articles we found via the pre-specified search terms and algorithm stated above (Table 1), we determined that 56 were eligible for this review (Figure 1). The majority of the articles were excluded because they studied internal chemical biosensors rather than external wearable biosensors. The sensors found in the articles included accelerometers, gyroscopes, multi-sensor systems, infrared devices, force sensors and eye tracking.

3.2 Overview of devices used in multiple sclerosis research

Application of wearable devices and biosensors in MS addresses unmet clinical needs in the detection and measurement of disability. Use of sensitive instruments to capture data pertinent to outcomes assessments in clinical trials offers the opportunity for participation in research to patients of diverse function and disability status. In a recent review from early 2017 on objective measurement of physical activity in multiple sclerosis, 83% of recent studies involved the use of accelerometers.[14] In this review, we identified a more diverse array of sensors, but still the majority of studies (47%) included use of accelerometers. Other sensors employed in trials or observational studies included gyroscopes (18%) and multisensors (11%). These differences in percentage over a short period of time are due to our inclusion criteria, with our review not being limited only to biosensor measurement of physical activity. Below we review the published experience of different categories of biosensors, including identified

strengths and weaknesses of different devices, and we outline future steps in the development of biosensing strategies in patients with MS.

3.3 Accelerometers

3.3.1 Overview

In recent years, use of accelerometers has drastically increased in the commercial and healthcare environments, most commonly to produce a "step count" assessment of daily activity. Accelerometers detect the displacement of the accelerometer through force sensors and converting the displacement into electrical signal thus measuring linear acceleration (Figure 2). Patients wear these devices on their hip, arm or thigh and these sensors can measure duration, frequency and intensity of physical activity. For chronic diseases like MS the goal of accelerometer assessments is to get a more comprehensive assessment of activity and function than is afforded by semiannual physical exams. Thus, it is not unexpected that there have been a growing number of studies in MS including accelerometer assessments [Table 2]. There have been multiple recent reviews of accelerometer use in study participants with MS in which the device was applied to measure disability through gait, balance, fall, and sleep assessments.[14-17] Overall the literature demonstrates promise for the development of user-friendly, objective measurement for physical activity and impairment of ambulation based on accelerometer sensors.[18]

3.3.2 Associations with Surveys

While surveys such as the Godin Leisure-Time Exercise Questionnaire (GLTEQ)[19] [20] or International Physical Activity Questionnaire (IPAQ)[21] are helpful in giving a general estimation of physical activity and have been validated as reliable measurements of physical activity, they are at an increased risk for recall bias and thus there are advantages to incorporating accelerometers as an objective measurement of physical activity and disability.[16] Accelerometers have shown moderate correlations (r^2=0.14-0.55) with self-reported surveys.[22-30] Furthermore, accelerometers have the ability to pick up temporal variability in physical activity that is difficult to capture with surveys. Accelerometer studies also demonstrate larger differences than have been demonstrated by survey-based data.[31]

3.3.3. Reliability and Accuracy

Test re-test reliability and accuracy are critically important to the overall utility of wearable devices in medicine. Good to excellent reliability has been demonstrated for accelerometers (Fitbit Flex, StepWatch, RT3) in people with MS with mild disability (ICC =0.76 to 0.86).[17 18 32] While reliability is extremely important, so is accuracy of the accelerometer as compared with manually counted steps. Step counts from the ActiBelt, ActiGraph, and StepWatch exhibited excellent accuracy in mild disability (95%-99%) when compared to true step count.[33 34] However, concern has been raised regarding decreased accuracy (87%-96%) associated with alterations in gait in participants with more severe disability and slower walking speed.[33 34] This can limit the ability to correctly evaluate patients with MS with severe disability. Thus, caution is needed for using this technology in those with high disability scores. [17 18 32-35]

3.3.4 Associations with EDSS

While the ultimate goal may be to show that sensor data is more sensitive than gold standard metrics, it is critical in the development phase to demonstrate associations between novel sensor outcomes and standard disability metrics. Moderate to good correlations (r^2= -0.37- -0.71, p= <0.001-0.36) between EDSS disability scores and accelerometer-based step counts have been reported (Table 2).[17 23 36 37] These results are encouraging, but also suggest that accelerometers are not a replacement of the EDSS but rather may add additional information missed by the EDSS. These potentially missed disability levels in the EDSS can be seen through a large variability in step count within higher EDSS category (e.g. EDSS = 6.0; step count = 1097-7152).[17] On the other hand, accelerometers may not capture upper body disability well using standard testing protocols that are gait focused. Indirectly, these devices may reflect visual or cognitive dysfunction if those deficits change level of physical activity, but accelerometers will likely play a complementary role is the assessment of MS patients rather than replace comprehensive physical exam based measures.

Overall most studies also showed lower step counts in those with MS compared to controls (Table 2). In studies with these assessments, lower activity/step counts were associated with increased disability scores, slower gait speed, increased risk for falls, and reduced cadence. [17 22 24 25 31 36 38-40] For example, Sosnoff et. al saw a correlation with EDSS and steps/day then took this one step further and saw a correlation between EDSS and number of falls in the past twelve months.[36]

Although these studies comparing accelerometers and EDSS are promising, due to the challenges in measuring physical activity in non-ambulatory patients, these studies limited enrollment to those with an EDSS between 0.0 – 6.5. This is a notable limitation in most applications of accelerometers and further development of technology and testing protocols are needed for severe disability in MS.

3.3.5 Association with MRI Phenotype

Accelerometers have also been shown to have correlations with MS imaging metrics such as white matter and gray matter brain volume further suggesting that these sensors are capturing disease specific effects[41 42]. Klaren et. al. examined the association between physical activity and brain volumetric measures in MS using MRI. Moderate to vigorous physical activity was found to be associated with normalized, white and grey matter volumes, as well as deep grey matter structures involved in motor and cognitive functions such as the pallidum, hippocampus, and thalamus.[41]

3.3.6 Variability in Accelerometer Use

Across publications there is heterogeneity in body location of the accelerometer, time spent wearing the accelerometer, epoch time, and type of accelerometers. Variability in accelerometers includes cost, size and weight, and the number of axes that the accelerometer detects. Devices studied in multiple sclerosis include ActiGraph 7164 (10), ActiGraph GT1M (2), ActiGraph GT3X (4), RT3 (2), TriTrac-R3D (1), CalTrac (1), StepWatch (2), SenseWear Mini (2), ActiBelt (1), and FitBit Flex (1). Uni-axial accelerometers only measure acceleration in one axis while tri-axial accelerometers measure acceleration in a 3-dimension field. Tri-axial accelerometers are increasing in

use in order to capture multidimensional data. Thus far, results from studies of tri-axial accelerometers have similar results to those using uni-axial accelerometers; both models of accelerometers show a decreased accelerometer count in correlation with greater disability.[17 18 34 36 39 41 43] A recent study by Block et. al. used two different tri-axial accelerometers to determine disability in MS and found an excellent test-retest correlation (ICC= 0.76) between these different accelerometers.[17] However, tri-axial accelerometers have not been shown to have higher reliability or higher correlations with EDSS as compared to uni-axial accelerometers. [17 23 36 37]

3.3.7 Longitudinal Use

Although accelerometers are one of the most commonly used measurement tools in MS, further studies are needed to validate the utility of longitudinal measurements. Only three studies we found indicated the benefit of long term follow up using accelerometers before and after an intervention, though the authors are aware of several ongoing studies not yet published that will examine repeated measurements over time.[44-46] One study by Motl et. al. showed significant linear changes in walking impairments and disability over a 2.5 year period.[45]

3.4 Gyroscopes

Impaired balance is a frequent symptom for patients with MS and can have profound impact on quality of life and ability to work. While certain physical exam maneuvers are designed to test for this (Romberg test, tandem walking as examples), there is a strong need for an objective measurement tool with high inter-

rater reliability to measure the degree of instability. Many digital devices now contain gyroscopes, which can record orientation and movement by measuring angular velocity (Figure 2). The use of a gyroscope allows for the determination of changes in posture as well as movement vectors (including acceleration and angle of force). This information can be used to identify falls, activities such as climbing and descending stairs, as well as the analysis of static balance and gait. [47 48] Thus, gyroscopes may provide objective measures of balance within and across individuals.[49]

Studies of reliability of gyroscope measurements in participants with MS have shown good to excellent test-retest reliability (ICC= 0.77-0.97).[50 51] As an example, in one study a gyroscope was used to calculate the mean angular velocity in the X,Y, and Z- axis during 3 consecutive Timed Up and Go (TUG) tests and found excellent reliability for the Mean Angular velocity in the X,Y, and Z- axis (ICC = 0.96-0.99).[51]

Gyroscope data has also been used to distinguish differences in gait patterns and tremors in participants and has been associated with severity of disease.[51-53] For example, Carpinella et al. applied gyroscope measurements to the finger to nose neurological exam maneuver to assess inter-rater variability and to improve this ordinal scale of measurement. A single hand inertial sensor was worn during the traditional finger-to-nose test and was used to analyze the tremor of the patient. This device-based measurement detected subtle abnormalities among patients who received a zero score on Fahn's tremor rating scale.[53] Other studies utilized gyroscopes to detect subtle differences on previously accepted standard of care

such as the 6 Minute Walk Test (6MWT) and the TUG.[51 54] Qureshi et. al. compared gyroscope gait data to the 6MWT and saw a correlation with subjective levels of fatigue and decreased gait speed.[54]

Gyroscopes are also now being included in new composite metrics, such as the Multiple Sclerosis Performance Test (MSPT).[55] The MSPT is a computer-based platform that provides quantitative data on walking speed, balance, manual dexterity, and visual function. In this paradigm a gyroscope within a tablet (iPad) is employed to create a metric of imbalance and rotation rates.[55]

As in the case of accelerometers, advantages of gyroscope technology include easy accessibility to devices with potential for continuous and/or remote monitoring. Because the gyroscope is lightweight and small, it can be easily incorporated into both the clinical exam and at home monitors. The angular information produced by gyroscopes can also enhance accelerometer data and provide us with insight regarding subtle gait and balance abnormalities in MS.[56]

Figure 2:

3.5 Multi-sensors And Other Sensors

3.5.1 Multi Sensors

While the majority of studies employed single-sensor applications of accelerometers and gyroscopes, multi-device approaches have also been investigated. Device integration is an important concept in which one sensor is used to enhance the interpretation of a second sensor. A study by Spain et al. utilized

body-worn motion sensors to detect significant differences in balance and gait between MS patients with normal walking speeds and normal controls.[57] In this study, they utilized six body worn sensors on different parts of the body that each collected both accelerometer and gyroscope data. These multi sensor systems worked together to detect differences in sway acceleration and axial trunk rotation, among other gait and postural parameters, that were missed during completion of the timed 25-foot walk and timed up-and-go test that are standard practice in MS care. Brodie et. al. also used a gyroscope to enhance the accuracy of accelerometer data by accounting for pelvic sway. Through this study, he showed that those with MS has significantly increased pelvic sway range to compensate for lower limb weakness and this sway is a possible contributor for errors seen in accelerometer studies.[56] Combining accelerometers with other devices has also been shown to better at home data collection and better detect changes in gait in MS.[58] In this study, they used a sensor with accelerometer and air pressure sensor integration to better measure a decrease in step count and maximum walking speed in people with MS.

These studies support the idea that greater phenotypic resolution of functional limitations may be derived from multisensor enhanced evaluations. This approach may be very helpful in evaluating mildly impaired patients that may be missed using only one biosensor.[39] Such improved detection of once-missed changes in patients' gait, balance, or ambulation in a multi-sensor system may in turn enable earlier intervention and inform clinical decision-making related to initiation or alteration of treatment.

3.5.2 Fatigue Sensors

Infrared markers have been used as a measurement of gait changes in MS due to fatigue.[59] This objective characterization of fatigue as compared to self-reported values may allow for a decrease in the effect of other factors upon the state of condition, such as undiagnosed depression. It also has the potential to be used as a measurement of the disease course as results change over time.[59] Changes in fatigue have also been measured using a multi-sensor system that involved two accelerometers, a portable EMG, body skin thermometer probe, muscle strength meter, ECG, and eye-movement detector. This pilot study was tested in two patients with MS showing that the device was user-friendly and did not interrupt daily activities, but future research is needed to determine the sensitivity and reliability of this multi-sensor system.[60]

These studies on fatigue were then taken one step further by using biosensors to measure autonomic regulation and looking for a correlation with autonomic dysfunction and fatigue.[61-64] By using EKGs, pupillography, and blood pressure and heart rate monitors, studies looked to use heart rate variability, blood pressure, and pupillary response as objective measurements of autonomic function. However, these studies showed variable results between fatigue and autonomic function. Some studies found a correlation between autonomic dysfunction and fatigue,[62 64] while other studies saw no correlation between autonomic function and fatigue.[61 63] Therefore, more research is needed on biosensor use to measure autonomic regulation to determine what accounts for this variability in results.

3.5.3 Grip Force Sensors

People with MS also show impairment in upper extremity function including abnormalities in grip strength. Grip strength is crucial in execution of Activities of Daily Living (ADLs) and other work-related tasks. Therefore, grip force sensors can be used as an objective measurement to analyze motor function in MS. Studies used a strain gauge and piezoelectric accelerometers to measure grip force, load force and speed of movement during simple day-to-day tasks. Studies consistently showed increased peak grip force as well as a longer time lag before peak grip force.[65-69] This increase in grip force was then shown to have a statistically significant correlation with EDSS score ($r=.41$, $p<0.04$).[68] Each of these studies was done in mildly affect MS patients (EDSS <5.5) thus indicating that over-gripping could precede more severe motor impairments in MS.

3.5.4 Eye Trackers

Eye tracking is another noninvasive technology that uses near infrared light to illuminate the eye to capture the cornea and pupil that is being used in MS to better diagnose the extent of disability in patients with MS. While MS is a heterogeneous disease, most patients (30-70%) will experience efferent visual dysfunction with significant impairment of quality of life, including diplopia, oscillopsia, and fixation losses.[70] Eye tracking biosensors can be used to detect subtle efferent vision abnormalities that could be missed in a normal bedside neurological exam. Efferent dysfunction such as abnormalities in smooth pursuits and saccadic movement can greatly affect the ability to work or read and can cause symptoms such as dizziness, gait impairment, and falls. Eye-tracking can help detect subtle cerebellar dysfunction leading to efferent vision dysfunction making it a more

sensitive test than currently accepted tests of cerebellar dysfunction.[71] Several studies have demonstrated that participants with MS have slower saccadic initiation compared to controls.[71 72] Because these study showed an increase in saccadic initiation in the absence of cognitive difficulties, they indicated that eye-motor disorders picked up by the eye-tracker can serve as a sensitive early marker of disseminated disease.

Moreover, efferent visual dysfunction captured by eye-trackers has been shown to be associated with overall disability in participants with MS and with cognitive measures such as the Symbol Digit Modalities Test (SDMT).[72] Poor performance on complex tests such as anti-saccadic movements have been associated with cognitive dysfunction in MS.[73]

3.5.5. Other Sensors

Although the direct link between stress and MS relapses is unknown, some studies have suggested a link between stressful events and rates of relapse.[74] Wearable biosensors that monitor electrodermal activity as well as heart rate variability offer the opportunity to measure the association of MS activity or symptoms with physiological correlates of stress.[75] This line of investigation may also afford development of real-time feedback and intervention using stress management techniques in patients who demonstrate worse clinical performance while experiencing stress

3.6 Clinical trials with wearable devices

At the time of review, there were 1,534 clinical trials found for multiple sclerosis on the clinicaltrials.gov website. Of these, 8 active trials incorporated wearable devices into the study design and five of those studies use biosensor outcomes as a primary or secondary outcome. (Table 3)

One clinical trial (Exploring the Effectiveness of Sensor based Balance Training on Patient Outcome Measures) is utilizing biosensors as a real time source of biofeedback for an intervention technique to better the gait and balance of individuals with neurological diseases including MS. The goal of this clinical trial is to use "Exergame" technology to provide real time information about patient's joint motion both in home and in clinic [Clincaltrials.gov NCT02777060]. Sensor information collected in this study is used as a rehabilitation strategy to improve postural stability, fix gait abnormalities, and decrease risk of falls in MS. These balance-training tests include ankle joint exercises and virtual obstacle tests.

Two studies used biosensors to determine and better the effectiveness of rehabilitation programs in MS (Table 3). As an example, the Task Oriented Upper Limb Training in MS trial focuses on using multiple outcome measures including accelerometer data to optimize upper limb rehabilitation programs. By using an ActiGraph accelerometer as an objective measurement and comparing it to outcomes such as the 9-hole peg test and Manual Ability Measurement-36, this study intends to provide evidence for intensity dependent upper limb training programs. Like the previous trial, the goal is to create better rehabilitation strategies for those with MS and measure the results of these new strategies and thus better the quality of life for those with severe MS. [Clinicaltrials.gov NCT02688231]

Lastly, there is currently a clinical trail (Algorithmic-Based Evaluation and Treatment Approach for Robotic Gait Training) that focuses on using wearable robotic exoskeletons (WRE) as a treatment tool in MS and other neurologic conditions. [Clincaltrials.gov NCT03057652]. The effectiveness of this WRE is measured using electromyography (EMG) in multiple tests with and without the WRE. In this, EMG is used to sense muscular activity with or without movement and thus can detect abnormalities in muscles and nerves. This biosensor is used to determine if the WREs are an effective treatment in people with MS. Using biosensors as a tool to measure the effectiveness of an intervention can help develop better methods of improving the quality of life of people with MS.

4.0 Conclusion

Wearable biosensors are user-friendly, non-invasive devices with potential to enhance the clinical evaluation of participants with MS.. Thus far, most devices studied have shown good to excellent test-retest reliability. Associations have been demonstrated between sensor data and standard physician and patient reported outcomes. . As the use of these devices expands, it will be important to determine best practices and to assess utility in longitudinal assessments in patients. Use of sensor-derived outcomes could also promote development of new interventions for patients with MS, particularly in the arena of rehabilitation.

Although the majority of articles available on biosensing in MS focus on the use of accelerometers, over time there has been expansion in the diversity of devices studied. Gyroscopes, infrared sensors, eye-trackers, grip force sensors,

electrodermal activity monitors and multi-sensor systems are being investigated as objective measurements of disability in MS.

Currently, there are several ongoing MS clinical trials that include biosensors in longitudinal studies. These studies further develop our understanding of the utility of these devices in detecting change in response to interventions and provide more evidence to incorporate biosensors into the clinical care of patients with MS.

5.0 Expert Commentary

Inclusion of wearable devices in the study of MS is increasing. Because this is a developing field, there are not yet standard protocols of application of these devices nor standard nomenclature. This poses difficulties ranging from challenges in identifying articles in literature searches to establishing best practices for observational studies or clinical trials. For each type of device there will need to be continued data quality investigations and standardization of best use practices. Attention will need to be given to considerations of the different settings of use including clinical trials and the real-world practice setting. Because these biosensors are noninvasive and for most are widely available, they hold great promise for generalizability to clinical practices.

Accelerometer-based outcomes provide promise as metrics of physical activity and performance outside the routine clinical setting. Their small, lightweight, user-friendly design enhances generalizability to real world settings. Accuracy in measuring disability is reasonable in mild to moderate MS, but becomes more problematic in those with very high disability scores. This is a limitation in the

capabilities of using only single sensor applications of accelerometers to measure disability in MS.

There is also a need to define best practices for commercially available devices including body location and type and model of accelerometer. In this review for example, the amount of variability in procedures for accelerometer use limited our ability to conduct a formal meta-analyses on reliability and associations with disability. In order to truly integrate accelerometer-based metrics in the evaluation of MS patients, additional studies are needed to identify best practices that yield the highest reliability with the most sensitive differentiation of physical ability and activity. Currently, the best reliability in accelerometer use in MS was found using a Step Watch Step activity Monitor on the right ankle for a seven-day period.

Of additional interest is how combination with other sensors can strengthen the utility of accelerometers in clinical applications. Multi-sensor systems with accelerometers included seem to provide better quality data and help correct for the inaccuracies that can be seen with accelerometer only studies.[56] This integration of biosensors holds great promise for improving overall accuracy and reliability of sensor-based metrics and providing a rich array of information on function

Gyroscopes, infrared monitors, eye-trackers, and EMG can all help provide ways to better measure disability in MS. From balance and gait abnormalities to vision abnormalities, these devices have been shown through multiple studies to provide reliable measurements of disability in MS and because these patients can have multiple different deficits, it is difficult for only one biosensor to pick of the extent of disability in patients. However, the breadth of evidence on these devices

are not as large as accelerometers and thus more research is needed on how to better use them as both measurements of disability and potential treatment tools. Also, due to the different types of function measured, as well as differing strengths and weaknesses, for each of these devices, multi-sensor studies can be beneficial to determine the true extent of disability in patients with MS.

The potential benefits of biosensors can also be extended beyond measuring disability in a controlled setting. For example, remote monitoring with biosensors can help provide clinicians with data collected in real world environments. This type of data can be used to provide more continuous assessments of function over time, rather than the snapshots afforded from semiannual physical exams.

On the other hand, there are many limitations to the current evidence on the use of biosensors. One of the biggest limitations to many studies of biosensors is they are limited to those with MS that are able to ambulate. Many studies focused on people with MS with an EDSS of 5.5 or less due to difficulties with measurements for those whom are unable to walk. These limitations are further exemplified by the inaccuracies shown using accelerometers in people with MS with severe disabilities. This also leads to inaccurate measurements for those that enjoy non-ambulatory activities such as swimming or cycling. Thus, although accelerometers and gyroscopes can provide useful information, it is important to not limit disability studies to these biosensors. Also, due to a lack of longitudinal studies, we are unable to say the benefit on these sensors to detect meaningful functional changes over time. This again becomes a concern if assessing a patient who previously was ambulatory and during the course of treatment becomes unable to ambulate. More

research is needed to determine the use of biosensors of an outcome measure over time. Another limitation is simplicity in the application of the biosensor and data delivery to the provider thus ensuring that the data received is easy to analyze and transparent in the results obtained. This includes incorporating a device that is both simple to apply to a clinical setting as well as simple for the provider to retrieve results. With this, includes determining an effective sampling rate. Biosensors can end up producing too much data, which can lead to noise affecting the ability to quickly determine changes from the patient's baseline. On the other side, too little data can lead to insensitivity and would overlook the real-time change that we hope to see. Finding this balance is critical in the wide spread use of these devices. Another large limitation of biosensors is the availability of these sensors. While accelerometers and gyroscopes and relatively common and cheap, other biosensors such as eye-trackers, infrared sensors, and multi-sensor systems are more expensive resulting in difficulties in wide spread accessibility.

6.0 Five-Year view

Due to the ever-advancing technology of biosensors, we expect there to be great progress in this field over the next 5 years. Within the last 5 years, accelerometers and gyroscopes technology has advanced with greater accuracy in the newest devices, and these devices have also become more accessible. We expect these trends to continue. Advancement in protocol development and applications of device use will allow accelerometers and gyroscopes to more accurately record function in those with higher disability scores. Continued development of

technology and software will allow these sensors to be more readily incorporated into clinical care of MS patients in the near future. For eye-trackers, improvements in detection frequency of events, reduced size of equipment, and decreasing costs will make these devices more accessible as a wide spread tool for people with MS. Multi-sensor systems will be increasingly incorporated for a multidimensional approach to evaluate disability in MS.

Application of wearable biosensors in the medical setting will help better the evaluation of physical function of people with MS. Future directions of research of critical importance also include longitudinal evaluations of device sensitivity and performance, continued development of multi-sensor systems, and creation of best practices for this type of research. The incorporation of biosensors into MS evaluations can be used to better detect dysfunction changes as well as develop new interventions in the treatment of different disabilities in people with MS.

7.0 Key Issues

- Development of biosensor-based outcome metrics in MS addresses unmet needs in the reliable and sensitive measurement of disability.
- Currently, the majority of articles available on biosensing in MS focus on the use of accelerometers and have promise in capturing patient function outside the clinical setting using sensors that are relatively cheap, user-friendly, and non-invasive.
- Most sensors studied in MS participations have demonstrated good to excellent test-retest reliability

- Other biosensors that hold promise as objective disability measures in MS include gyroscopes, infrared sensors, eye-trackers, grip force sensors, ectodermal activity monitors, and multi-sensor systems, but more studies creating a more robust sample size are necessary
- There remains to be a need for additional research in emerging new biosensors, multi-sensor use, as well as agreement in most effective settings and body locations for many biosensors

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Declaration of interest

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References of Importance

14** Casey et al: This article is a great review of using biosensors to measure physical activity in MS

45** Motl 2013: This is one of the few published studies that uses biosensors in a longitudinal study. Researchers can use this study in future longitudinal studies on biosensors

29* Ng This is one of the earliest papers using biosensors to measure disability in MS.

58* Spain: This article is a good example of incorporating a multi-sensor system into measuring disability in people with MS

Figure and Table Legends:

Figure 1: Eligibility Determination for Review: Flow Chart for included articles

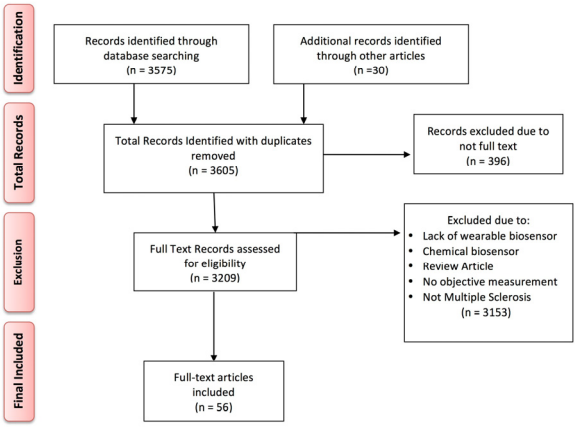

Figure 2: Gyroscope angular motion vs accelerometer linear motion

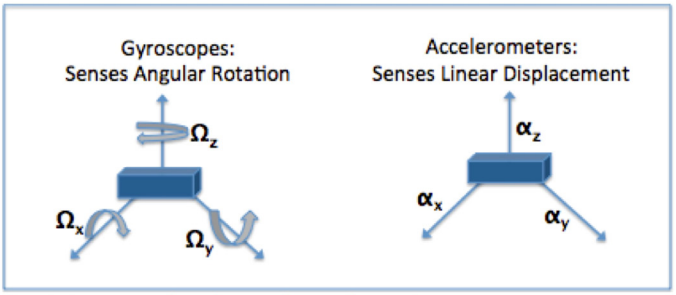

Figure 2: Gyroscope angular motion vs accelerometer linear motion

Table 2: Accelerometer studies: The use of accelerometers in MS has been widely studies. However, as seen above there remains a slight variability in the use of accelerometers as a metric in MS.

PwMS - Patients with Multiple Sclerosis; RRMS – Relapsing Remitting Multiple Sclerosis; PPMS - Primary Progressive Multiple Sclerosis; SPMS – Secondary Progressive Multiple Sclerosis; HC – Healthy Control EDSS – Expanded Disability Status Scale; PDDS – Patient Determined Disease Steps; FSS – Functional Systems Score; GLTEQ – Godin-Leisure Time Exercise Questionnaire; 7DPAR – 7-Day Physical Activity Recall, MMSE – Mini Mental State Examination; MS-RS – Multiple Sclerosis Rating Scale; EXSE – Exercise Self Efficacy, IPAQ – International Physical Assessment Questionnaire; MW – Minute Walk; T25FW – Timed 25 Foot Walk; TUG – Timed Up and Go; MSWS-12 –Multiple Sclerosis Walking Scale-12; SWAmini – SenseWear Mini

Table 3: Table 3: Clinical Trials: Wearable devices are becoming more common as an intervention in Multiple Sclerosis **Indicates studies that used biosensor measurements as an Primary "and" or "or" secondary outcome
HC: Healthy Controls; EMG: Electromyography; WRE: Wearable Robotic Exoskeleton; TUG: Timed Up and Go T25FW:Timed 25 Foot Walk

Table 1: Search Terms

List Of Search Terms used
"sensor" OR "biosensor" OR “wearable biosensor” "Accelerometer" OR "gyroscope" OR "gait" OR "gait analysis" OR "eye-tracking" OR "physical activity" OR “fatigue” OR “grip force” AND "multiple sclerosis"

Table 2: Accelerometer Studies in Multiple Sclerosis

	Type of Sensor/Model	Location of sensor worn	# of days worn	Epoch Time	Type of MS	EDSS Range (Median)	Primary results
Ng 1997	TriTrac-R3D Tri-axial	Waist	Waking Hours x 7 days	1 min	18 Total 10 RRMS 8 PPMS/SPMS	1.5 – 6.0 (3.0)	- Activity counts in pwMS were less than the sedentary control group and had a modest correlation with the questionnaire - No correlations between the activity counts and any clinical measures (EDSS, FSS)
Busse 2004	StepWatch Tri Axial	Elastic band on right ankle	24 hours/day x 7 days	NA	10 MS, 10 Parkinson's 10 primary muscle disorder	2.0-6.5 (4.0)	- Excellent test-retest in step counts in neurological patients. - Step counts were significantly different in all patient groups compared to HC
Motl 2006	ActiGraph 7164 Uni-axial	Elastic Belt on non dominant hip	Waking hours x 7 days	1 min	196 Total: 174 RRMS 19 SPMS 3 PPMS	NA	- Physical Activity had a direct relationship with self-efficacy and enjoyment portions of a questionnaire
Motl 2006	ActiGraph 7164 Uni-axial	Elastic Belt on non dominant hip	Waking hours x 7 days	1 min	30 Total: 26 RRMS 2 SPMS 2 PPMS	(4.0)	- Activity counts were correlated with GLTEQ, 7dPar suveys, and EDSS and MMSE
Gosney 2007	ActiGraph 7164 Uni-axial	Elastic Belt on non dominant hip	Waking hours x 7 days	1 min	196 Total: 174 RRMS 19 SPMS 3 PPMS	NA	- Activity counts in pwMS were less than HC - Activity counts were moderately correlated with GLTEQ, symptoms score, and pedometer output
Kos 2007	ActiGraph	Elastic Belt on non dominant wrist/ankle	24 hours/da7 x 3 days	1 sec	19 Total MS	(5.5)	- Activity counts were moderately correlated with questionnaire and differences in wrist and ankle were not significant
Snook 2008	ActiGraph 7164 Uni-axial	Elastic Belt on non dominant hip	Waking hours x 7 days	1 min	80 Total: 62 RRMS 15 SPMS 1 PPMS 2 Benign	(Mean: 3.9)	- Activity counts in pwMS were strongly correlated with MS-RS and Motor subscale of MS-RS. 5 other subscales (brainstem, sensory, mental, elimination, and EXSE) were moderately correlated.
Hale 2008	RT3 Tri-axial	Waist belt on central back	Waking hours x 7 days	1 min	47 Total: 11 MS 20 Stroke 7 Parkinson 9 Controls	NA	Good test-retest reliability, but had significant differences between 3 day & 7 day data
Weikert 2010	ActiGraph 7164 Uni-axial	Elastic Belt on non dominant hip	Waking Hours x 7 days	1 min	269 RRMS	PDDS 0.0-6.0 (2.0)	- Activity counts were strongly correlated with GLTEQ, IPAQ, MSWS-12 and PDDS
McAuley 2010	ActiGraph 7164 Uni-axial	Elastic Belt on non dominant hip	Waking hours x 7 days	1 min	196 Total: 174 RRMS 19 SPMS 3 PPMS	PDDS 0.0-6.0 (2.0)	- Higher activity counts were correlated with stronger physical, self-evaluative, and social outcome expectations
Motl 2010	ActiGraph 7164 Uni-axial	Elastic Belt on non dominant hip	Waking Hours x 7 days	1 min	269 RRMS	PDDS: 0.0-6.0 (2.0)	- Activity counts were indirectly associated with overall symptoms via fatigue and depression in RRMS
Motl 2011	ActiGraph 7164 Uni-axial	Elastic Belt on non dominant hip	3 six-minute walking (6MW) tests	1 min	24 Total MS 21 RRMS 2 Benign MS 1 PPMS	PDDS 0.0-4.0 (1.0)	Step count was highly accurate in moderate/fast walking pwMS and HC. - There was a small degree of underestimation of step counts during slower walking in MS and controls.

Dlugonski 2011	Actigraph 7164 Uni-Axial	Elastic Belt on non dominant hip	Waking hours x 7 days	1 min	21 RRMS	PDDS: 0-5 (1.0)	Internet intervention resulted in moderate increases in accelerometer activity counts
Prakash 2011	Actigraph GT3X Tri-axial	Left hip	Waking hours x 7 days	1 min	45 Total MS 42 RRMS 3 Progressive	2-6 (Mean: 4.1)	Activity count was associated with increased coherence between hippocampus & posteromedial cortex
Motl 2012	ActiBelt Tri-axial	Belt around waist	6MW Test	1 min	51 Total MS	2.0-6.5 (4.0)	Step count was highly accurate in pwMS with mild disability, but was overestimated in pwMS with moderate and severe disability.
Sosnoff 2012	Actigraph GT3X Tri-axial	Elastic Belt on non dominant hip	Waking hours x 7 days	NA	75 Total 66 RRMS 9 Progressive	2.0-6.5 (4.0)	- Step count in the fall group was less than the nonfall group - Step count was significantly correlated with EDSS
Motl 2013	ActiGraph 7164 Uni-axial	Elastic Belt on non dominant hip	Waking Hours x 7 days x6 mos	1 min	269 RRMS	PDDS: 0.0-6.0 (2.0)	- Physical activity, self-efficacy, walking impairment, and disability had linear changes over 2.5 years
Pilutti 2013	ActiGraph GT3X Tri-Axial	Elastic Belt on waist	Waking hours x 7 days	1 min	82 Total MS 65 RRMS 10 SPMS 7 PPMS	PDDS: (2.0)	- Internet intervention resulted in moderate but not significant increases in accelerometer activity counts
Sandroff 2014	StepWatch (bi-axial) vs ActiGraph GT3X (Tri-axial)	Elastic band on Right ankle Vs Elastic Belt on right hip	6 one-minute walking tests	3 sec	63 Total MS	0.0-6.5 (4.0)	- StepWatch and ActiGraph both demonstrated highly accurate measurement of steps taken under Comfortable Walking and Fast walking conditions, but the Actigraph had increased inaccuracy in the slower walking condition
Balantrapu 2014	Actigraph GT3X Tri-Axial	Elastic Belt on non dominant hip	Waking Hours x 7 days	1 min	84 Total 69 RRMS	2.0-6.5 (4.5)	- PwMS with leg spasticity had worse ambulation as measured by 6MW, T25FW, TUG, MSWS- 12, O_2 cost of walking, average steps/day, and walking velocity
Kahraman 2015	Caltrac	Elastic Belt on non dominant hip	Waking Hours x 7 days	NA	52 Total 34 RRMS 9 CIS	0.0-3.5 (1.5)	- Activity counts in minimally impaired pwMS were associated with walking speed, endurance, gender, employment status, and quality of life and were less than the HC.
Klaren 2015	Actigraph GT3X+ Tri-axial	NA	Waking Hours x 7 days	NA	39 Total 30 RRMS 9 PPMS/SPMS	(4.5)	- Moderate-strong physical activity was associated with white matter volume and gray matter volume
Fjeldstad 2015	ActiGraph GT1M Bi-axial	Elastic Belt on hip	8am-9pm x7days	1 min	12 RRMS	0.5 – 6.5 (2.5)	Physical Activity was Negatively correlated with EDSS
Pau 2016	Tri-axial accelerometer Gyroscope & Magnetometer	Elastic Belt on low lumbar level	T25FW	NA	105 Total MS	0-6.5 (Mean: 2.2)	Most disabled Class 3 pwMS were characterized by slower gait speed and reduced cadence - T25FW was moderately correlated with MSWS-12 score in all groups
Kruger 2017	SenseWear Mini Armband	Elastic band on Middle of left triceps	Waking Hours x 7 days	1 min	26 Total MS	1.5-6.0 (4.0)	- Activity counts in pwMS were less than HC and had a moderate correlation with IPAQ
Block 2017	1. Fitbit Flex 2. ActiGraph GT3X 1. Tri-axial 2. Tri-axial	Elastic band on Non-dominant Wrist	At all times except while swimming	NA	99 Total MS	0.0-6.5 (Mean: 4.1)	- Excellent test-retest between Fitbit, Actigraph, and manual step counts during a 2MW test - Step counts were lower in progressive than RRMS and was associated with EDSS score

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Table 3: Clinical Trials in Multiple Sclerosis using Wearable Devices

Clinical Trial Name	Study Objective
Exploring the Effectiveness of Sensor-based Balance Training on Patient Outcome Measures	-Provide real time information about joint motion in people with MS using Exergame biosensors Outcomes: change in balance and gait speed using wearable biosensors**
A Low-cost Virtual Reality Gaming Platform for Neurorehabilitation of Hemiparesis	- Measure effectiveness of rehabilitation program in MS using biosensors Outcome: changes in accelerometer data during treatment**
Task Oriented Upper Limb Training in MS	- Optimize upper limb rehabilitation programs in MS using biosensors Outcome: changes in accelerometer data during treatment**
Sleep, Physical Activity and Multiple Sclerosis Symptoms in Pediatric Multiple Sclerosis	- Examine the relationship between sleep and physical activity in pediatric MS using biosensers Outcome: Accelerometer data comparing sleep and physical activity**
Algorithmic-Based Evaluation and Treatment Approach for Robotic Gait Training	- Gait training using WREs in people with neurological conditions Outcomes: EMG changes with and without WRE**
Monitoring of Multiple Sclerosis (MS) Participants With the Use of Digital Technology (Smartphones and Smartwatches) - A Feasibility Study	-Assess the feasibility of remote participant monitoring using digital technology in participants with MS and HC Outcome: Compliance with completing tests
Comprehensive Fall Prevention and Detection in Multiple Sclerosis	- Fall prevention strategies in people with MS. Some participants will receive a wearable fall detector Outcome: Changes in falls and fall related injury
Robot-assisted Gait Training on Mobility in Severely Disabled Multiple Scleosis Patients	- Test the feasibility of WRE in a group of progressive severely disabled MS patients Outcome: Timed 25 foot walk (T25FW)
Wearable Lower Extremity Exoskeleton to Promote Walking in Persons With Multiple Sclerosis	-Investigate the use of WRE to help people with MS to walk Outcomes: TUG & T25FW Time Changes

Table 3: Clinical Trials: Wearable devices are becoming more common as an intervention in Multiple Sclerosis **Indicates studies that used biosensor measurements as an Primary "and" or "or" secondary outcome
HC: Healthy Controls; EMG: Electromyography; WRE: Wearable Robotic Exoskeleton; TUG: Timed Up and Go T25FW:Timed 25 Foot Walk