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Biosensors to monitor MS activity

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Abstract: Advances in wearable and wireless biosensing technology pave the way for a brave new world of novel multiple sclerosis (MS) outcome measures. Our current tools for examining patients date back to the 19th century and while invaluable to the neurologist invite accompaniment from these new technologies and artificial intelligence (AI) analytical methods. While the most common biosensor tool used in MS publications to date is the accelerometer, the landscape is changing quickly with multi-sensor applications, electrodermal sensors, and wireless radiofrequency waves. Some caution is warranted to ensure novel outcomes have clear clinical relevance and stand-up to the rigors of reliability, reproducibility, and precision, but the ultimate implementation of biosensing in the MS clinical setting is inevitable.

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The neurological exam is arguably the most elegant in all of medicine, yet our standard tools for evaluating multiple sclerosis (MS) patients remain antiquated. J. Madison Tyler designed the first reflex hammer in 1888[1] and Henrich Rumpf[2,3] published on the use of the tuning fork for vibration sense in 1889. Recent advances in sensor technology and the computer control industry afford the MS specialist the opportunity to measure neurological function in exciting new ways that may enable the capture of subclinical progression and the prevention of adverse outcomes.

Biosensors by definition convert physiological information into electrical signals. Biosensors generally fall into one of two categories: small molecular sensors used inside tissues or external, wearable sensors. Data from sensors can be digitized, as is the case in most external wearable sensors. In MS, the most common wearable used in published studies to date is the accelerometer,[4] but many other types of sensors have been used including gyroscopes and electrodermal sensors. Molecular or microscopic biosensors have not yet fully emerged in the MS field, but a few nanobiosensors have been reported including those detecting MS-related micro-RNAs[5] or protein biomarkers in the cerebrospinal fluid.[6]

Accelerometers

Along the more well-beaten path of biosensing in MS are the growing number of studies employing accelerometers, ideally augmented by gyroscopes, to track step counts or activity levels. These studies attempt to capture ambulatory function or high-intensity activity in real-world settings and to complement standard clinic assessments of walking performance. A fundamental principle of a new measure is test–retest reliability. Generally, accelerometers have held up fairly well in this regard (intra-class correlations ranging from 0.76 to 0.86).[7–9] Tri-axial accelerometers have been shown to be more reliable than uniaxial accelerometers.[7] Accuracy of these devices for step counts is very good for MS participants with low disability but becomes an issue with those of higher disability levels.[10] Associations of accelerometers with physical activity surveys have been modest to moderate and correlations with the Expanded Disability Status Scale (EDSS) scores have ranged from $r^2 = -0.4$ to -0.7.[4]

Significant remaining challenges for accelerometer studies include the (1) array of products and protocols that have been used without consensus yet on best practices for the field and (2) limited studies with multi-year longitudinal analyses. The latter limitation is a common theme for most biosensing applications in MS, given the youth of the field, but is a critical one. Many things from biosensors to biomarkers have been shown to associate with the EDSS, but few have shown robust sensitivity and specificity for detecting small changes in function over time.

Gyroscopes

Gyroscopes have been used in approximately 20% of research studies on biosensing in MS.[4] They have shown good test–retest reliability.[11,12] They have been

used to improve the accuracy of accelerometer data, detect falls, digitize the timed up and go test, quantify gait, and measure tremor.[4,11–17] Gyroscopes are being used in the Multiple Sclerosis Performance Test[18] and the Floodlight Open (https://floodlightopen.com/en-US/) suite of MS performance tests. Both of these suites of digital testing employ sensors in mobile devices to assess upper and lower limb function as well as balance. For Floodlight, the gyroscope, accelerometer, and magnetometer within a smart phone are leveraged for assessment of fine motor and gait function as well as balance, stamina, and mobility.

Other forms of biosensing

Other types of sensors that have been used in MS patients include grip sensors,[19] electrodermal sensors (to detect stress and fatigue),[20] and surface[21] or portable[22] electromyograph (EMG). A number of clinical trials from the past few years list biosensor outcomes from rehabilitation trials to more standard pharmacological studies exploring sensor data as secondary or exploratory outcomes (clinicaltrials.gov).

At the 2019 annual meeting of ACTRIMS, work defying the above two categories was presented on ambient biosensing that was neither related to a molecular nor wearable device. Dr Dina Katabi presented her work from MIT using wireless radio reflection signals in the home to detect research participant motion, sleep patterns, and falls. In this paradigm, the study subject does not have to wear or charge any device. For this wireless sensing of movement, the key element is a device the size of a laptop or Wi-Fi router that emits low-power radio frequency signals. These waveforms change when they come into contact with the individual's body and any movement creates changes in the signal waveform.[23] Notably, these signals can be used to detect the user's motion through a wall.[24] The modified signals are collected and then processed by artificial intelligence (AI)-based algorithms. In the WiTrack2.0 algorithm from Dr Katabi's group, up to five different individuals, including static and moving individuals, can be tracked in the same space.[25]

Wireless sensing has appeal for detecting falls, mobility level within the home, and sleeping patterns. Specific movement patterns such as gait features may also be extracted.[26] But obvious privacy issues arise with continuous monitoring of movements within someone's home and data protection becomes essential as it is determined who could have access to these types of data. While these detailed within-home observations of patient activities are an obvious example of security risk, all investigators of biosensing projects need to consider the potential privacy vulnerabilities. Kumar and Lee,[27] in 2012, outlined several key considerations for devising security protections when using wireless medical sensor networks: (1) assessing the scale and setting of the network (within home, within hospital, or other medical facility); (2) identifying the types of sensors involved—body-worn, environmental, or device-based (phone, tablet); (3) what are the backend services that store patient data; and (4) who is interacting with the data and through what mechanism are they accessing data. Various security threats have been identified along this pathway of collecting and transmitting biosensor data[27] and schemes have been devised to prevent "eavesdropping" and hacking, but there is also the general principle of privacy that must be addressed. Who can access or own patient physiologic data? How can principles of consent be preserved? Regulations in countries across the globe are still trying to catch up.

Validation of new biosensor assessments

The optimal approach to validate new technology for clinical use is a multistep, rigorous process. First, extraction of sensor data through more standard or AI-based signal processing must be related to a ground truth about the disease state to ensure clinical significance. Unsupervised machine learning or other agnostic approaches have a place for generating new perspectives and hypotheses, but generally for establishing novel outcome measures, the new technology must be formally related to known measures of clinical relevance. Second, reproducibility and reliability need to be established. Precision of measurement will ultimately determine utility. If within-patient test–retest variability is higher than variability across patients or higher than change over short time intervals, then it will be limited to no utility of the new outcome measure. Finally, sensitivity to change over time must be established. This is perhaps the most challenging to determine. Finding associations in cross section are much easier, but to advance the field of MS therapeutics, in particular for progressive MS, we need measures sensitive to change over the short term.

Biosensing in practice

Factors that will determine the adoption of biosensors into MS clinical research and practice include reliability, sensitivity to changes in function, degree of disruption to patient life or clinical work flow, cost and the ethics of confidentiality, and patient safety. Practical considerations include establishing standards for data

quality and collection for these devices as well as determining the best sampling rates for different types of data. How often do patients have to be tested to capture desired signal and how much is just going to create noise and burden? Real-time delivery of analyzed data will be the most helpful to physicians. To achieve this goal, software will need to be provided (along with the hardware) that is commercial grade in terms of reliability and either embedded with sensor device or readily loaded onto a PC or mobile device. Bluetooth or other wireless connectivity to transfer data is essential.

Multi-sensor systems are likely to rise to the top of the biosensing world as they can provide complementary data for a richer representation of a particular motion or event. The expanding array of potential biosensors and exponentially increasing publications make it inevitable that neurologists in the coming decades will see discrete biosensor data filtering into their clinics, but the seatbelts and guard rails of the fast-moving phenomenon are the tried and true tools of clinical research, enforcing the rules of reliability and clinical utility to determine which biosensors rise to the top.

Declaration of Conflicting Interests

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