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# Brain monitoring technologies in neuroscience clinical research- Significant potential with the advancement of remote monitoring through the use of sensors, wearable devices, and mobile technology

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**Introduction:**

The advancement in the miniaturization and cost-effectiveness of sensors and circuitry has driven innovation in wearable and microsensor technologies for health monitoring. These developments enable the creation of devices capable of measuring complex health parameters in non-specialist and remote environments. In this article, we explore various innovations in brain monitoring, including portable and wearable devices for direct measurement of brain electrical activity, as well as tools that assess related functions such as sleep patterns, gait, cognition, voice acoustics, and gaze tracking. Although further scientific validation is necessary, we suggest that the current understanding of these methods is sufficient to consider them as exploratory tools in clinical research. The extensive and frequent data they generate could offer valuable insights, justifying their inclusion in clinical study designs.

Understanding brain function is an incredibly complex task. As Emerson M. Pugh famously remarked, "If our brains were simple enough to understand, we'd be so simple that we couldn't comprehend them." Given this complexity, a range of tools have been developed to assess various aspects of brain activity. These tools include direct measures of brain function, such as electroencephalography (EEG), as well as indirect measures like sleep patterns, gait, cognition, and gaze analysis.

This blog delves into the rapidly growing field of remote-monitoring sensors, wearable devices, and mHealth (mobile health, which involves using mobile devices like smartphones and tablets in healthcare). It explores how these technologies can be harnessed for large-scale clinical trials and patient monitoring, extending their utility beyond just market approval.

**Wearable and Mobile Applications:**

A sensor is a component or device that detects and quantifies physical or chemical properties from its environment, converting this information into an electrical output. Microsensors, which are compact sensors incorporating both electrical and mechanical elements, are often referred to as microelectromechanical systems (MEMS). These devices are typically manufactured using integrated circuit techniques with silicon or similar materials. Wearable devices, which include one or more sensors, are designed to be worn on the body, such as through wristbands, belts, headbands, adhesive patches, contact lenses, or glasses. In the context of brain monitoring, an example of a wearable device could be a headband equipped with sensors to measure EEG signals from the frontal cortex. The integration of reliable, high-performance microsensors in medicine is increasingly important for patient health monitoring, personal wellness, and clinical research.

The advancement in sensor and circuitry miniaturization has driven the rapid growth of wearable technology. Thanks to the development of more compact, efficient, and intelligent processors and sensors, there's been a significant increase in the availability of cost-effective consumer devices for personal health and wellness. The market for connected health and wellness devices, valued at approximately $123.2 billion in 2015, is projected to reach $612.0 billion by 2024.

Consumer applications for brain training through neurofeedback have gained popularity. These applications use wearable headsets to measure EEG brain activity and provide users with real-time feedback to promote brain health. For instance, users might receive visual representations of EEG activity that reflect both efficient (beta wave) and less efficient (slow wave) brain activity during attention training. Typically, we can't distinguish between different brain wave patterns on our own, but neurofeedback provides immediate insight, allowing users to learn how to modify their brain activity. Over time, this helps users consciously adjust their brain wave patterns even when they are not using the device. These applications are available for managing stress, anxiety, and improving focus and concentration.

**Application to Clinical Trial:**

The application of wearable and remote devices, along with mHealth apps, in clinical trials offers promising opportunities for monitoring and evaluating treatment interventions. Given the stringent regulatory standards in this field, ensuring the validity of outcomes data from these technologies requires thorough examination. The Critical Path Institute's Electronic Patient-Reported Outcome (ePRO) Consortium has recently provided a detailed review and set of recommendations on the evidence necessary for selecting a wearable device or remote sensor for clinical trials, particularly for supporting labelling claims. These recommendations are summarized later in the article.

This blog specifically focuses on wearable devices and mobile apps that track electrical brain activity and related aspects such as sleep patterns, cognitive function, gaze analysis, and speech acoustics. Many of these technologies are emerging and show potential for use in clinical trials, particularly for exploratory endpoints and to complement other study endpoints measuring similar concepts. A summary of the main technologies discussed, along with their validation status and evidence supporting their use in clinical trials, is provided in the accompanying table.

**Remote- monitoring devices and their applicability for use in clinical trials**

| Device type | Examples of relevant devices | Measurements | Usability | Strength of recommendation for clinical trial use |
|---|---|---|---|---|
| Portable EEG headband | MUSE (Intraexon Inc., Toronto, Canada)<br><br>Emotive EPOC (Emotive Inc., Sydney, Australia) | Event-related brain potential | HIGH: regular use for short intervals of time daily | B |
| Wrist-worn actigraphy device | Act iWatch 2 (Philips Respironics, Murrysville, PA)<br><br>Motion watch 8 (CamNtech, Cambridge, UK) | Sleep quality, quantity and circadian rhythms | HIGH: regular use for multiple days | A |

| | | | | |
|---|---|---|---|---|
| Peripheral arterial tone wrist/hand-worn device | Watch PAT (Itamar Medical, Caesarea, Israel) | Sleep architecture | HIGH: regular use for short intervals of time daily | B |
| Forehead worn sleep monitor | Sleep Profiler (Advanced Brain Monitoring, Carlsbad, CA) | EEG, EOG, EMG, ECG | MEDIUM: Use of periods of one or two consecutive nights at intervals throughout study | A |
| Non- contact sleep sensor | Beddit 3 sleep monitoring system (Apple, Cupertino, CA)<br><br>S + sleep sensor (ResMed, San Diego, CA)<br><br>ES contact-free sensor (Early Sense, Ramant Gan, Israel) | Sleep quality and quantity and circadian rhythms | HIGH: regular use for multiple days | C |
| Wearable gait monitor | Kinesis Health Technologies (Dublin, Ireland)<br><br>McRoberts (The Hague, The Netherlands)<br><br>APDM Wearable Technologies (Portland, OR)<br><br>MC10 (Boston, MA) | Detailed gait measurements | HIGH: regular use for short in-clinic performance tests<br><br>HIGH: regular use for multiple days<br><br>HIGH: regular use for short in-clinic performance tests<br><br>HIGH: regular use for multiple days | B |
| Gait monitoring insole | F-Scan system (Tek scan Inc., South Boston, MA) | Detailed gait measurements | MEDIUM: use for short in-clinic performance tests | C |
| Cognitive function | Project EVO (Akili Interactive Labs, Boston, MA) | Multitasking | HIGH: regular use for at-home tests | B |
| Mobile eye tracking solutions | Senso Motoric Instruments (SMI, Teltow, Germany)<br><br>Tobii | Eye tracking endpoints | HIGH: regular use for at-home tests | B |

| | | | | |
|---|---|---|---|---|
| | (Stockholm, Sweden)<br><br>Right Eye (Bethesda, MD)<br><br>Gaze Capture (MIT, Boston, MA) | | HIGH: regular use for at-home tests | C |

**NOTE -** This sample is chosen from the expanding range of available devices to demonstrate the confidence levels for various concepts. A Grade B or C does not disqualify the device; rather, it signifies that a newer concept is employed and still requires additional validation.

A: Ready for deriving trial endpoints based on reported validation evidence and/or current use.
B: Suitable for exploratory use and supplementary data, with a need for more validation and experience.
C: The approach shows promise but requires further research and evaluation before making strong recommendations for clinical research use.

**Considerations for evidence to support Device use and Endpoint Development:**

In clinical trials, study endpoints are specific characteristics or variables that indicate a patient's well-being, functionality, or survival. Endpoint descriptions outline how and when measurements are taken, the calculation methods, rules for handling missing data, and the analysis approach. In the absence of formal regulatory guidelines, the Critical Path Institute's ePRO Consortium has provided consensus recommendations on the evidence needed for selecting wearable devices and the endpoints derived from their data.

When employing sensors or devices to measure health outcomes in clinical research, it is crucial to establish the reliability and validity of the collected outcome data, ensure that the outcome measures accurately reflect the concepts defined by the clinical trial objectives, and confirm the suitability and interpretability of the endpoints derived from this data. While some evidence may come from market clearance or certification processes, such clearance or certification is not mandatory for devices used in clinical research.

- **Reliability-**
  To verify the consistency of a device, both intra-device and inter-device reliability should be evaluated through test-retest assessments using the same device and different units of that device. Generally, this is measured using the intraclass correlation coefficient. Device manufacturers are required to show that their products are manufactured in accordance with a quality system, ensuring that devices are consistent across batches and align with the reliability data provided.

- **Concurrent Validity-**
  Concurrent validity is crucial for verifying that a method accurately measures what it is intended to assess. This is usually achieved by comparing the results with a well-established gold standard that is recognized as a reliable measure of the concept in question.

- **Content Validity-**
  To ensure that the endpoints identified are meaningful to patients and reflect relevant outcomes for the disease or treatment being studied, it is crucial to demonstrate their importance. If the significance of these outcomes is not well established, their content validity can be assessed through qualitative data collection from patients, healthcare professionals, or caregivers.

- **Ability to detect change-**
  In clinical trials, it's crucial that outcome measures and derived endpoints are sufficiently responsive to detect changes when they occur. This responsiveness is typically validated through controlled studies where an intervention is known to produce a change in the outcome being measured.

- **Endpoint interpretability-**
  To ensure an endpoint is appropriate for use in a clinical drug submission, it is crucial to comprehend what constitutes a meaningful change. This involves understanding the degree of change in the endpoint that can be considered clinically significant for the patient. This significance is often represented by the minimal important difference (MID) or minimally clinically important difference (MCID), which reflect the smallest change that is considered valuable to the patient or that differentiates between responders and non-responders. Established methods are available to estimate these values and define responders. The subsequent sections of this article will review validation evidence supporting emerging wearable and remote monitoring technologies that aim to assess various aspects of brain activity either directly or indirectly.

**Electroencephalography [EEG] and Evoked Potentials [EP]:**

Hans Berger was the first scientist to record human EEG data in 1924. Since then, the core principle of EEG has remained the same: electrodes positioned on the scalp detect voltage changes caused by ionic currents in brain neurons due to brain activity. The recorded signals are processed through filtering and computerized analysis, which aids in visualizing the data through techniques such as quantitative EEG (qEEG) or EEG mapping.

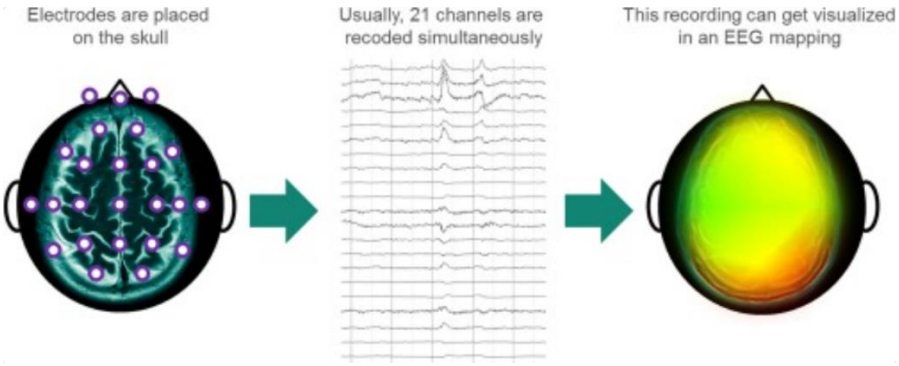


*Fig.1: The principle of EEG-mapping*

EEG mapping has been used in clinical research to examine brain activity patterns induced by psychotropic drugs and mental disorders, which show characteristic signatures in quantitative EEG (qEEG). However, qEEG is not yet recognized as a surrogate endpoint in central nervous system (CNS) drug development. The concept of "pharmaco-EEG," which involves analysing EEG patterns in response to psychotropic medications, remains relevant for assessing cerebral bioavailability, time- and dose-related efficacy, and the bioequivalence of various drug formulations.

Another promising application of qEEG is in evaluating brain responses to different external stimuli and sensations, such as pain. Given that pain is typically measured through subjective patient reports, which are susceptible to high placebo effects, qEEG could offer a more objective method for assessing pain.

**Wearable devices to measure EEG and EP data:**

Wearable EEG devices are commonly worn around the forehead and use dry electrodes to gather brain activity data, which is then processed by the device's firmware to provide a continuous EEG signal trace. In the realm of health and wellness, mobile EEG technology is mainly applied in two areas. One area involves using brain activity data to control devices or enable communication, exemplified by the "Mind Speller" developed by researchers at the Catholic University of Leuven and IMEC in Belgium. The other area focuses on brain-training applications through neurofeedback, primarily for consumer use.

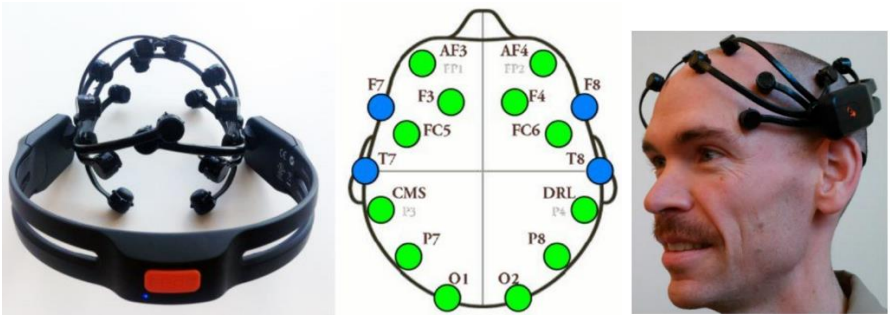


*Fig.2: The EMOTIV EPOC EEG device.*

Several portable EEG headband devices are available for consumer product development, which often come with established software development kits for integration with smartphones and PCs. Notable examples include the MUSE (Intraexon, Toronto, Canada), Emotive EPOC (Emotive, Sydney, Australia), and Zen Zone (Neuro Sky, San Jose, CA). For instance, the MUSE device features a headband with seven sensors placed across the forehead and behind each ear. Recent advancements also include in-ear EEG recording through electrodes positioned in the outer ear canal and concha, allowing for continuous and discrete recording. While initially not designed for clinical research, many of these devices offer software development kits that enable researchers to access raw signal data for investigative purposes.

Providing a highly portable solution for frequent data collection from patients in remote locations, such as their homes, along with continuous mobile monitoring, holds the potential to translate neuroscientific insights into practical clinical and everyday applications. However, to ensure that the data collected is reliable, accurate, and precise, especially for exploratory studies and regulatory submissions, it's crucial to assess the quality of EEG traces obtained through these methods. A significant factor in this assessment is the number of electrodes and their attachment to the skin. Traditional clinic-based EEGs typically utilize 21 electrodes placed across the scalp, allowing for the detection of electrical activity across various brain regions. In contrast, portable devices, such as a forehead headband, primarily measure activity from the frontal cortex and depend heavily on a secure fit to maintain electrode contact and minimize disturbances that might affect the EEG signals due to movement. Device firmware may help mitigate some of these disturbances by filtering out certain artifacts.

There is limited research validating the reliability of these portable systems for event-related brain potential (ERP) studies. However, existing research suggests these devices show promise. For instance, a study comparing the Emotiv EPOC headband with a research-grade EEG system (Neuroscan v. 4.3) found that while the headband's electrode placement stability led to fewer acceptable measurement epochs, the Emotiv headband still provided reliable ERP data for various ERP peaks in children aged 6–12 under different listening conditions. The Emotiv headband, which samples EEG at 120 Hz from 14 electrodes and filters artifacts within a 0.2–45 Hz bandwidth, demonstrated better alignment with full EEG system measurements compared to earlier studies in adults, which had shown only moderate associations.

Another validation study involving MUSE technology indicated that the portable headband accurately measured the N200, P300, and reward positivity ERP components in experimental settings completed in under 10 minutes, highlighting the utility of low-cost portable EEG systems in field and clinical research.

Artifact and noise filtering are critical for obtaining reliable data from portable EEG headsets. Biological artifacts, such as those from eyelid and eye movements, pulse artifacts from nearby blood vessels, scalp muscle activity,

body movements, and sweat/skin artifacts, can often be filtered out, though eyelid and eye movement artifacts are more challenging and may be controlled through techniques such as fixed gaze or artifact subtraction. This was evidenced by a study using MUSE and NeuroSky headbands, which struggled to detect blinking signals. Technical artifacts, including electrostatic and electromagnetic interference, also pose challenges.

The use of portable headsets and earpiece devices for remote and continuous EEG measurement represents an emerging area with significant potential, though further research is needed to validate the reliability and accuracy of data obtained through these methods.

**Pain Measurement:**

EEG data has demonstrated efficacy in providing objective assessments of pain. Individuals with chronic pain often show increased alpha and theta power in spontaneous EEG readings, alongside reduced ERP amplitudes in response to various stimuli. PainQx, based in New York, NY, employs advanced, portable EEG technology and proprietary algorithms to analyse and interpret brain activity related to pain. This objective measure of pain could complement traditional self-report scales and patient-reported outcomes, and may assist in evaluating the immediate effects of analgesic and narcotic medications.

Using EEG mapping, PainQx quantifies activity in brain regions associated with pain perception, known as the "Pain Matrix," while excluding unrelated areas. This method isolates, identifies, correlates, and assigns weights to these areas to provide an objective assessment of a patient's pain level. This technique appears to differentiate between high and low pain states in chronic pain, similar to how heart rate differentiates acute pain levels. Future research will determine if it can more accurately identify responders compared to current subjective pain scales.

**Alzheimer's disease:**

Event-Related Potentials (ERPs) offer an objective means of examining brain processes. In a standard ERP experiment, participants listen to a sequence of tones that includes frequent (standard) tones, occasional infrequent (target) tones, and rare unexpected (distractor) tones. Participants are instructed to respond only to the infrequent target tones. This setup generates an ERP waveform composed of various components that produce both positive and negative deflections. The P300 component, characterized by a positive deflection occurring around 300 milliseconds after the target tone, is associated with attention and working memory. This component has been demonstrated to be useful in identifying clinically significant cognitive changes, such as those seen in Alzheimer's disease. Although ERPs provide immediate physiological measures of cognitive processes and are valuable for exploratory studies, they are not yet widely recognized as surrogate endpoints in major clinical trials.

**Traumatic brain injury/ contusion:**

Mild brain contusion, a common injury in sports like American football, rugby, and soccer, currently lacks an easy-to-use and objective method for assessing disease stage and outcomes. At present, diagnosis and management rely on subjective tools and self-reported symptoms, which limits their clinical effectiveness. However, companies such as Cerora (Bethlehem, PA) have developed biosensors, primarily utilizing EEG technology. When combined with traditional cognitive tests, these biosensors could potentially enhance researchers' and clinicians' ability to make more informed decisions regarding the disease stage and outcomes. Nevertheless, there is a lack of data supporting this approach, leaving its specificity and sensitivity uncertain.

**Epilepsy:**

Mobile EEG technology has the potential to enable long-term monitoring in outpatient or home settings. If these wearable devices can be used for extended periods without causing discomfort, they could be particularly useful in studying epilepsy, where seizures can occur unpredictably and need to be recorded outside of clinical environments. Continuous monitoring might be beneficial for detecting and characterizing seizures, identifying subtle seizures that might otherwise go unnoticed by patients, or assessing seizure frequency when patients present with seizure-like symptoms. This capability is crucial for clinical trials evaluating new treatments, as it provides objective data on seizure activity. Long-term EEG monitoring in ambulatory settings has already shown promise in diagnosing and managing challenging cases that don't respond well to standard in-clinic EEG assessments. For instance, it can help distinguish between nocturnal epilepsy and other sleep disorders involving abnormal movements, as well as accurately characterize seizure types and frequencies. However, further research is needed to confirm if this approach is both reliable and practical.

**Portable Sleep assessments technologies:**

We dedicate roughly a third of our lives to sleep, making it a crucial component of our daily existence. It is well established that there is a two-way relationship between sleep disturbances and clinical diseases, affecting and being affected by them. Despite ongoing debates regarding the precise definition, diagnosis, and measurement of sleep, a straightforward behavioural definition describes sleep as "a reversible state characterized by disengagement from and reduced responsiveness to the surroundings."

In clinical drug development, assessing sleep and its impacts can be crucial, as changes in sleep patterns may directly or indirectly indicate treatment effects. The significance of various objective measurements of sleep depends on the specific goals of the clinical investigation. For example, monitoring sleep architecture and continuity can be valuable for evaluating brain health in relation to neurodegenerative diseases. Sleep spindles-brief bursts of high-frequency brain activity during non-rapid eye movement sleep-have been linked to cognitive decline in Parkinson's disease, while a reduction in slow wave sleep is associated with Alzheimer's disease.

**Sleep outcome measures/ parameters:**

Sleep architecture describes the fundamental structure of normal sleep. In adults, sleep typically alternates between rapid eye movement (REM) sleep and non-REM (N-REM) sleep, with N-REM sleep making up approximately 75-80% of the sleep period. A complete sleep cycle includes four stages of N-REM sleep followed by REM sleep, with these cycles becoming progressively longer throughout the night.

Beyond just sleep architecture, factors such as sleep quality, quantity, circadian rhythm, sleep consolidation, regularity, and napping are crucial in evaluating sleep and wake patterns. Common metrics for assessing sleep quality and quantity include sleep onset latency, wakefulness after sleep onset, sleep efficiency, number of awakenings, and total sleep time.

The choice of technology and methodology for evaluating these parameters varies based on the specific sleep aspect being studied. The International Classification of Sleep Assessment provides guidelines that are widely adopted in the biopharmaceutical industry, particularly when sleep data is used as a key endpoint in regulatory drug approvals.

**Polysomnography:**

Polysomnography (PSG) is widely regarded as the gold standard for evaluating sleep architecture. This comprehensive, overnight assessment involves monitoring multiple physiological parameters, including EEG, electrooculography (EOG), and surface electromyography (EMG). Additionally, PSG can measure pulse oximetry, respiratory effort, and core temperature. Due to its complexity and the extensive equipment required, PSG has

traditionally been confined to specialized sleep laboratories and requires the expertise of trained technicians for data analysis and interpretation.

Despite its status as the gold standard, PSG has limitations, especially concerning cost and the necessity for access to specialized labs. One significant issue is the "first night effect," where sleeping in an unfamiliar setting may impact sleep measurements. Furthermore, manual data analysis can lead to high variability between different raters.

To address the cost and reliance on specialized services associated with PSG, there has been a focus on developing alternative technologies for sleep assessment in nonclinical environments. The following review explores key technologies in this area.

**Remote sleep assessment: Actigraphy:**

Actigraphy involves using an accelerometer to monitor gross motor movements, based on the principle that a lack of movement suggests sleep, while movement indicates wakefulness. This technique, which began in the 1970s, has seen the development of various devices equipped with advanced algorithms to filter out environmental noise. These devices have been validated against polysomnography (PSG) and are now trusted tools for evaluating sleep quality and duration outside of clinical settings. Their minimal impact on daily life and ability to provide long-term data on sleep and activity make them popular in both research and drug development for tracking changes in sleep patterns.

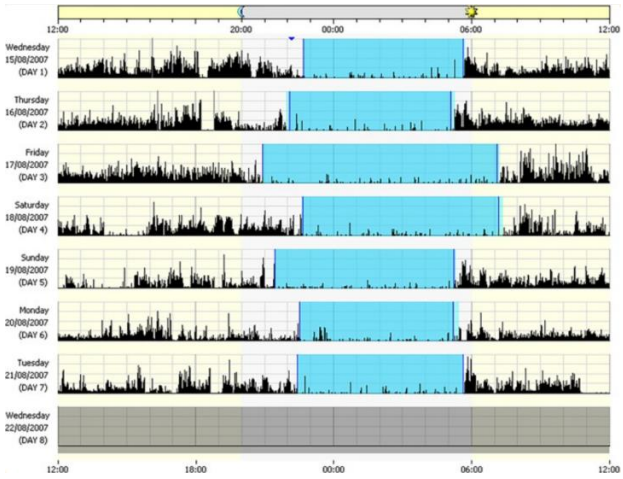


*Fig.3: An actogram showing changes in daily activity and sleep patterns. Black bars represent periods of activity. Shaded blue areas represent resting/ sleep periods.*

Actigraphy has shown promise in accurately estimating sleep parameters like quality, duration, and circadian rhythms. However, it is not validated for assessing detailed sleep architecture, including REM and N-REM sleep. While actigraphy results typically align well with polysomnography (PSG) in healthy adults (over 90% correlation), the correlation can drop to around 50% for certain parameters in individuals with insomnia, such as sleep onset latency. Different actigraphy devices and their corresponding firmware and software have varying sensitivities to movement and immobility. A higher sensitivity to immobility helps the device detect sleep periods, whereas sensitivity to movement helps identify wakefulness. Generally, actigraphy is quite effective at predicting sleep but less accurate at detecting wakefulness, which can lead to an overestimation of total sleep time. When choosing a device for clinical research, it is crucial to select one that has been validated for the specific population under study.

**Actigraphy with additional physiological channels:**

Recent advancements in actigraphy devices now include the ability to measure various physiological parameters such as heart rate, respiration rate, skin conductance, skin temperature, and blood oxygen levels. This allows for a more comprehensive assessment of sleep architecture, beyond just sleep quality and duration. One example of such a device is the WatchPAT (Itamar Medical, Caesarea, Israel), which, in addition to actigraphy, measures peripheral arterial tone (PAT). Originally designed for home-based sleep apnea monitoring, emerging research indicates that PAT shows a high level of agreement with polysomnography data and can reveal distinct patterns corresponding to different sleep stages. This capability helps in distinguishing between REM and N-REM sleep, as well as differentiating lighter sleep stages from deeper, slow-wave sleep.

**Ambulatory PSG and EEG:**

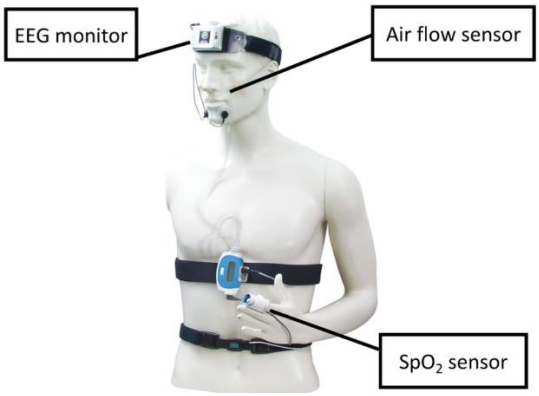


*Fig.4: Sleeper Profiler EEG device to assess sleep architecture and continuity.*

While more comprehensive testing can be conducted at home using ambulatory PSG, which tracks multiple parameters such as EEG, EOG, EMG, ECG, pulse rate, airflow, respiratory movement, and oxygen levels, this method can be costly and may require specialized teams for implementation and management. An alternative device, the Sleep Profiler (Advanced Brain Monitoring, Carlsbad, CA), offers a practical solution. Worn on the forehead overnight, it monitors EEG, EOG, EMG, ECG, pulse rate, head position, head movement, and snoring through various sensors secured with a headband (see Fig 4). Research has shown that sleep biomarkers obtained over one or two nights using this device are valid compared to PSG, making it suitable for both clinical and research purposes. This allows for monitoring of sleep architecture and continuity over multiple nights at home or continuously in an ICU setting. Automated sleep staging algorithms linked to the Sleep Profiler have demonstrated reliability when compared to manual assessments.

**Non-contact sensor technology:**

A new class of sleep assessment tools has recently emerged, which claim to monitor sleep parameters without requiring users to wear any devices. One example, the Beddit 3 Sleep Monitoring System (Apple, Cupertino, CA), utilizes a flexible piezoelectric film sensor placed beneath the bed sheet. This sensor is capable of detecting subtle body forces on the bed, which it interprets to estimate pulse (heart pumping), breathing effort (thoracic expansion), and overall body movement. Validation studies comparing heart rate estimates to ECG and breathing effort to the respiratory effort signal in PSG have shown promising results, though further research is needed. The Beddit system connects via Bluetooth to a mobile phone hub, transmitting data to a central server where algorithms estimate heart rate, respiratory variation, activity, sleep stages, and stress reactions. Another device using a similar piezoelectric sensor, the ES contact-free sensor (Early Sense, Ramat Gan, Israel), has demonstrated good reliability in estimating total sleep time compared to PSG.

An alternative approach, the S+ sleep sensor (ResMed, San Diego, CA), employs a bedside monitor that detects ultralow-power radiofrequency waves to track the user's movements in bed, including chest expansion and relaxation during respiration, as well as general body movements like positional changes, arm twitches, and shrugs. The device utilizes proprietary algorithms to identify different sleep stages, such as wakefulness, light sleep (N1, N2), deep sleep (N3), and REM sleep. However, robust validation studies are still required for this method to be considered useful in clinical research.

**Gait Assessment:**

Gait analysis is crucial for understanding the progression and treatment of neurodegenerative diseases. Research has highlighted that gait abnormalities can serve as predictors for the risk of developing dementia, with emerging evidence from clinical practices and studies showing a strong link between gait and cognitive function. This relationship is also evident in Parkinson's disease, where there is a connection between overall cognitive abilities and various gait-related measures, including pace, turning, and postural stability.

In-clinic evaluations of temporal and spatial gait parameters are often conducted using pressure pad systems such as Gait RITE and Zeno Walkway, or with 3D motion capture solutions like the Vicon marker-based camera system. While these systems provide accurate gait assessments, they are typically used in specialized centres, which might limit their applicability in large-scale clinical trials.

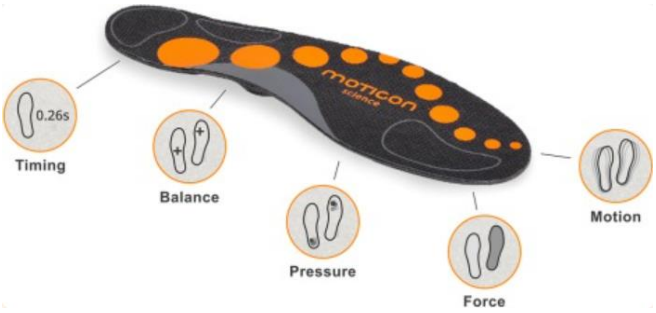


*Fig.5: Moticon insole system for gait analysis.*

There is a growing interest in methods that allow for the remote measurement of gait parameters in real-world settings, as these could offer a more comprehensive and informative view of gait compared to a single clinic visit. Innovative technologies are emerging that enable robust, objective, and sensitive measurement of a wide range of gait parameters, both in clinical settings and remotely. Companies such as Kinesis Health Technologies, McRoberts, APDM Wearable Technologies, and MC10 are developing user-friendly systems that can objectively assess and estimate gait parameters like cadence, gait speed, step duration, and more, using multiple sensors and sophisticated algorithms.

Innovations such as pressure sensors and accelerometers embedded in footwear insoles, like the F-Scan system and Moticon's insole, represent a patient-centred approach for frictionless gait assessment in everyday environments. Studies using the Moticon insole, for example, have shown it to be reliable and valid for collecting gait data. Additionally, the use of 3D depth cameras from motion-based gaming platforms, such as Microsoft Kinect and Intel RealSense, has shown promise in capturing gait parameters through simple in-clinic tests, potentially reducing the need for specialized centres.

One challenge in gathering detailed free-living gait assessment data is the ability to accurately interpret the context in which the data is collected. Variations in external conditions, such as the type of terrain, footwear, clothing, the dimensions and layout of living spaces, accessibility to outdoor areas, and weather conditions, can all influence remote gait assessment.

**Cognitive function testing:**

Cognition encompasses the abilities to perceive, react, process, understand, store, retrieve information, make decisions, and generate appropriate responses. Disruptions in cognitive function, such as impairments in attention, concentration, and memory, are commonly associated with various mental disorders. Testing cognitive function can identify the brain mechanisms involved in these symptoms and assess the effects of treatment. In clinical trials, cognitive function is often measured under laboratory conditions using computerized test batteries, such as the CDR system (Bracket, Arlington, VA) and the CANTAB system (Cambridge Cognition, Cambridge, UK).

**Nonlaboratory measurement of Cognition:**

Advancements in cognitive function testing have traditionally relied on validated platforms, supported by extensive normative data. However, laboratory-based tests are often constrained to smaller studies with infrequent assessments. Recently, new methods have emerged that facilitate more frequent testing in non-laboratory environments and among larger patient populations. These innovations enable ongoing assessments during clinical trials and post-market evaluations.

One novel approach involves using video game-based applications to measure cognitive functions such as reaction times, memory, and problem-solving skills. An example is Project: Evo, a game developed by Akili Interactive Labs. This mobile application is designed to measure and enhance interference processing, an essential component of executive function, by creating a gameplay environment where users' abilities to filter out distractions during focused tasks are evaluated. This game-based platform is being tested globally in various patient populations, including those with ADHD, autism, depression, and traumatic brain injuries. Notably, Pfizer has reported that gameplay outcomes on this platform successfully differentiated between amyloid-positive and amyloid-negative older adults, indicating its potential as a non-invasive biomarker for Alzheimer's disease. Shire is also exploring its use in ADHD clinical trials.

Smartphones have shown great potential for delivering visual cognitive function tests remotely. Initial studies indicate that these methods can produce reliable cognitive function estimates with strong concurrent validity compared to traditional approaches. Apple's Research Kit platform allows the development of diverse patient performance assessments, including cognitive tests such as the paced visual serial addition test, spatial memory test, and simple reaction time test. Although some validation studies have been conducted, further research is necessary to ensure the reliability and validity of these measures.

Additionally, wearable devices like smartwatches offer the potential to administer and measure cognitive tests remotely. Cambridge Cognition has extended their lab-based testing solutions to include remote cognitive assessments via wearable devices. Preliminary research using a two-back symbol memory test on the Microsoft Band 2 supports the feasibility of cognitive testing through wearables.

**Eye Tracking:**

Eye-tracking metrics serve as invaluable, non-invasive tools for understanding brain functionality and cognitive processes. For instance, analysing gaze patterns aids in evaluating attention and cognitive strategies; variations in pupil size, influenced by noradrenaline, are associated with arousal and mental activity; and blink frequency, regulated by dopamine, correlates with learning and goal-driven behaviours.

The field of pupillometry is increasingly recognized for its ability to indicate physiological states. Research on animals has demonstrated that fluctuations in pupil diameter correspond with rapid changes in adrenergic and cholinergic activity within the cortex. Additionally, in studies examining mental fatigue and task disengagement, pupil measurements have proven effective in gauging task disinterest.

Spontaneous blink frequency offers an indirect assessment of dopamine activity in the central nervous system, with observed decreases following the administration of dopamine receptor antagonists. Infant studies have revealed that eye movement patterns can serve as early diagnostic indicators for autism, noting that children on the autism spectrum tend to focus more on geometric designs than human faces.

Assessing fixation stability and saccadic movements—quick eye movements that abruptly shift the point of focus—has shown clinical relevance for various central nervous system disorders, including Huntington's disease,

progressive supranuclear palsy, and Parkinson's disease. In the initial stages of dementia, recording saccadic eye movements may assist in distinguishing between Lewy body dementia and Alzheimer's disease.

The use of eye tracking is garnering heightened interest as a potential biomarker for brain injuries. Conducting studies on treatments for traumatic brain injury presents challenges, such as population heterogeneity due to insufficient diagnostic and classification methods and the absence of robust, objective outcome measures. The failure of the ProTECT III and SyNAPSe clinical trials, which investigated progesterone treatment for acute traumatic brain injury, has been partly attributed to the lack of adequate biomarkers. However, eye tracking has been proposed as an objective biomarker for brain injuries and concussions.

**Portable eye tracing technology:**

Eye tracking remains largely confined to a select few specialized companies that provide validated eye-tracking technology. Among these, Senso Motoric Instruments (SMI, Teltow, Germany; now owned by Apple) and Tobii (Stockholm, Sweden) are recognized as industry leaders. They offer both lab-based camera systems and more portable options, such as glasses and virtual reality headsets. Another emerging provider in this field is Right Eye (Bethesda, MD), which offers a cloud-based solution that has demonstrated reliability in estimating certain eye-tracking parameters.

*Fig.6: A volunteer wearing an EEG cap in front to the Tobii Pro Spectrum eye tracking platform*

Researchers from the Massachusetts Institute of Technology, the University of Georgia, and the Max Planck Institute for Informatics have created a mobile app called Gaze Capture. This app, which runs on Apple devices, presents a sequence of dots for the user to follow with their eyes. The front-facing camera on the device records eye movements as the user completes the task. The app uses machine-learning algorithms that have proven to predict gaze with high accuracy on both smartphones and tablets. This method allows for the remote collection of extensive eye-tracking data in large-scale studies.

As eye-tracking technology is increasingly used to analyse consumer behaviour and is integrated into gaming and virtual reality platforms, there is likely to be ongoing investment in this field. These advancements will enhance the capabilities and accessibility of eye-tracking technology, particularly benefiting applications in clinical research.

**Voice acoustical analysis:**

Research has been exploring the capture and analysis of speech patterns in patients, particularly through acoustical analysis. Studies indicate that acoustical changes in the voice may serve as early indicators of Parkinson's disease, even in its extremely early stages. Additionally, in cases of depression, certain voice characteristics, such as speaking rate and pitch variability, have been found to correlate with traditional measures of disease severity, like the Hamilton Depression Rating Scale. A methodology study comparing acoustical measurements from recordings made with advanced laboratory equipment to those obtained simultaneously via telephone using an Interactive Voice Response system found the data to be highly comparable. This suggests the potential for large-scale longitudinal testing in home

environments. Moreover, recent developments include phonation tests for Parkinson's patients in mobile clinical research apps on platforms like Apple Research Kit and Android, highlighting the feasibility of using these cost-effective techniques in extensive clinical trials.

**Conclusion:**

The rapid growth in the market for wearable devices and remote sensors is largely fueled by advancements in sensor miniaturization, circuit design, and the enhanced functionality and processing capabilities of mobile devices like smartphones and tablets. In the realm of healthcare, particularly brain monitoring, these advancements create opportunities to develop and utilize innovative devices for measurements that were traditionally limited to clinical settings. Significant technological progress is evident in portable EEG monitoring and other brain function areas, such as sleep assessment, gait analysis, cognitive function testing, eye tracking, and voice analysis.

While wrist actigraphy for sleep parameter measurement is already established and widely accepted in clinical trials, many of the technologies discussed in this article are still emerging and require ongoing research for validation and proof of utility. It is recognized that further studies are necessary to better understand the reliability and validity of these new technologies and to generate the knowledge needed to interpret new endpoints derived from their data. Nevertheless, there is sufficient understanding of how these approaches can be implemented as exploratory tools in clinical studies, offering valuable insights due to the rich and frequent data they produce, which supports their inclusion in clinical research protocols.

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