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Evaluation of movement and brain activity

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Full conflict of interest

Mark Hallett is an inventor of patents held by NIH for an immunotoxin for the treatment of focal movement disorders and the H-coil for magnetic stimulation; in relation to the latter, he has received license fee payments from the NIH (from Brainsway). He is on the Medical Advisory Boards of CALA Health and Brainsway. He has research grants from Allergan for studies of methods to inject botulinum toxins, Medtronic, Inc. for a study of DBS for dystonia, and CALA Health for studies of a device to suppress tremor. Rodger Elble has served as a consultant for Applied Therapeutics, Cadent, Cavion, Cydan, Five Microns, Jazz, Merz, Neurocrine Biosciences, Osmotica, Praxis Precision Medicines, and Sage in the design and execution of clinical trials for essential tremor. He serves on advisory boards for the International Essential Tremor Foundation and the Neuroscience Research Foundation of Kiwanis International, Illinois-Eastern Iowa District.

Fay B. Horak has a significant financial interest in ADPM Wearable Technology, an ERT company that may have a commercial interest in wearable technology. This potential conflict has been reviewed and managed by OHSU. Dr. Horak also consults for Neuropore, Sanofi, and Takeda.

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Abstract

Clinical neurophysiology studies can contribute important information about the physiology of human movement and the pathophysiology and diagnosis of different movement disorders. Some techniques can be accomplished in a routine clinical neurophysiology laboratory and others require some special equipment. This review, initiating a series of articles on this topic, focuses on the methods and techniques. The methods reviewed include EMG, EEG, MEG, evoked potentials, coherence, accelerometry, coherence, posturography (balance), gait, and sleep studies. Functional MRI (fMRI) is also reviewed as a physiological method that can be used independently or together with other methods. A few applications to patients with movement disorders are discussed as examples, but the detailed applications will be the subject of other articles.

Keywords

EEG; MEG; EMG; fMRI; kinematics; accelerometer; posture; gait; sleep; coherence; movement; movement disorders

1. Introduction

There are many different tools and techniques for evaluating movement disorders. They can be used for diagnosis and for assessment of severity that can be useful for monitoring progression or therapy. There are general principles for their use and specific guidelines; describing them is the purpose of this chapter. Some applications are noted as examples, but the full details of how individual movement disorders are addressed will be found in subsequent chapters. The first sections on electromyography (EMG) and kinesiology show how movements can be measured. The posturography and gait section discusses quantitative assessment for these special and important movements. The next section deals with brain activity and the various ways it can be evaluated. Brain activity controls the muscle activity and this process can be assessed with corticomuscular coherence, the next topic. Polysomnography uses all these methods and more to evaluate sleep. The last section deals with functional magnetic resonance imaging (fMRI), another important tool to investigate brain activity which can be used on its own or together with EEG. A special section on direct recordings of deep brain activity, now possible during operations for deep brain stimulation, will be a separate, associated manuscript.

2. Electromyography

Electromyography (EMG) is a valuable technique for the analysis of movement disorders. Muscles make movements, and EMG measures the activity of muscle and, therefore, is also a measure of alpha motoneuron activity. Needle EMG is typically used for the analysis of neuromuscular disease. As a general rule, when dealing with movement disorders, it is assumed that those aspects are normal; the questions are different. In this situation the

questions asked include what muscles are active and what is the pattern of activation. The term kinesiological EMG is sometimes used.

EMG data can be measured with surface, needle, or wire electrodes. Surface electrodes have the advantages that they are not painful, and they record from a relatively large volume of muscle producing a good average of its activity. Recordings are made with pairs of surface electrodes, typically placed near the middle of the muscle belly about 2 or 3 cm apart. Bellytendon recording is usually not appropriate since recording volume would be too large and pickup would include nearby muscles. A European consortium called SENIAM (Surface Electromyography for the Non-Invasive Assessment of Muscles) has proposed detailed technical guidelines for use of surface EMG (seniam.org). Needle electrodes have the advantage that they are more selective, but they are stiff and can only be used for movements that are close to isometric. Needle electrodes are used when there is question of peripheral origin of the movement disorder where there would be characteristic findings such as fasciculations. Pairs of fine wire electrodes have the advantage of selectivity similar to that of needle electrodes but are flexible and permit free movement with only little pain.

Another way of recording surface EMG is with high-density arrays of electrodes, which can show possible changes in spatial location of activity within a muscle as the task changes. For example, activity of several lower extremity muscles was recorded with an array of 64 electrodes with 8 mm spacing arranged in 5 columns and 13 rows (Schlink et al., 2020). When normal individuals vary locomotor speed from walking to running, the spatial spread and center of gravity of activity in the muscles change. Similarly, the center of activation in the biceps brachii muscle changes with level of force (Borzelli et al., 2020). It is also possible to decompose the signal to determine the firing behavior of a number of the motor units. For example, this method was used to identify instability of motor unit behavior in patients with multiple sclerosis with impaired gait (Davis et al., 2020).

It is important to avoid movement artifact, which can contaminate the EMG signal. Low-frequency content of the EMG signal can be removed or dampened with filtering, and this will remove much of the movement artifact. Movement artifact is mostly in the range of DC to 10 or 20 Hz. Surface EMG has significant power in this range also, but the peak power is at about 100 Hz, so the filtering of power below 20 Hz still leaves most of the EMG power. When surface electrodes are used, their impedance should be reduced to 10Kohms or less. This will reduce electrogenesis at the electrode-skin interface caused by slight movements. To reduce the impedance sufficiently, it is usually necessary to clean and abrade the skin.

The amplitude of EMG provides information about the magnitude of the central nervous system command. For this purpose, the magnitude in mV can be used but only thoughtfully. Since the electrodes are not in a “standard” position and there will be varying relationships between the skin surface and the muscle belly, the absolute measurement has ambiguous meaning. There are two ways of standardizing the measurements. One is with respect to maximal voluntary EMG output, but maximum output itself might be difficult to obtain. For example, persons can generally not produce a maximum contraction of triceps surae. The other method is relative to a maximum compound muscle action potential (CMAP) produced by nerve stimulation. When using these standardized methods, the values in

mV should be reported in addition to ratios to make sure the reader understands the measurements. EMG is occasionally used as a measure of force, but this should only be considered approximate since the relationship between EMG amplitude and force is not exact, may change in different circumstances, and is often not linear (Solomonow et al., 1986). Moreover, the relationship can vary in pathology (Zhou et al., 2007). Comparing EMG amplitude intersubject, normalizing to the ensemble peak or average amplitude is best (Yang et al., 1984).

In analyzing the EMG for amplitude, it can be beneficial to rectify and smooth the recording. This process produces an “envelope” of the EMG signal. The amplitude of the envelope can be used as the magnitude of the EMG, and for a burst of EMG, the integrated area of the envelope is a good measure. In the situation of a tremor, then the successive envelopes of EMG form a curve like a sinusoid, and the record can be analyzed with a frequency analysis to get information about the frequency content of the signals driving the tremor.

Since numerous muscles act on any joint, it is highly recommended to record from at least two muscles with antagonist actions to understand the pattern. For voluntary movements, the EMG patterns are characteristic and vary with the speed of movement (Berardelli et al., 1996). A slow, smooth movement is characterized mainly by continuous activity in the agonist. A movement made as rapidly as possible, a so-called ballistic movement, has a triphasic pattern with a burst of activity in the agonist lasting 50 to 100 msec, a burst of activity in the antagonist lasting 50 to 100 msec, and return of activity in the agonist often in the form of a burst.

In different disorders of voluntary movement, there are characteristic abnormalities of attempted rapid movement. With cerebellar lesions, there is prolongation of the first agonist and/or antagonist EMG bursts. With parkinsonian bradykinesia, there is abnormal patterning, with multiple bursts having the appearance of repetitive cycles of the triphasic pattern to complete the movement. With dystonia and athetosis, there is excessive activity, including co-contraction activity, in the antagonist. Excessive activity also overflows into muscles not needed for the action. EMG burst length can be prolonged.

Inspection of the EMG signal of an involuntary movement reveals, first, whether the movement is regular (usually a tremor) or irregular. There are occasionally unexpected findings in such an analysis. For example, rhythmic EMG activity can appear irregular if the amplitude varies. The duration of the EMG burst associated with an involuntary movement can also be measured; specific ranges of duration are associated with different types of movements. Specification of duration in the range of 30 to 300 msec by clinical inspection alone is virtually impossible due to the relative slowness of the mechanical events compared with the electrical events. Finally, antagonist muscle relationships can be specified as synchronous, asynchronous, or alternating (reciprocal) (Fig. 1).

There are three EMG patterns that may underlie involuntary movements (Hallett et al., 1994). Two patterns are similar to the voluntary patterns for slow and ballistic movements described above. The third pattern resembles the burst occurring in many reflexes, such as

the H reflex. The EMG burst duration is 10 to 50 msec, and EMG activity in the antagonist muscle is virtually always synchronous.

Different types of myoclonus can be characterized by one of the three types of patterns, and the EMG can help make the diagnosis (Fig. 2). Dystonia and athetosis show mostly tonic patterns. Chorea is characterized by a wide variation of EMG burst durations encompassing all three patterns. In tic, there can be ballistic or tonic patterns. These patterns are summarized in Table 1.

There can also be brief lapses in tonic innervation that are clinically called asterixis or negative myoclonus (Shibasaki, 1995, Toro et al., 1995). Clinically, the lapses appear as an involuntary jerk superimposed on a postural or intentional movement (Fig. 3). Careful observation should show that the jerk is in the direction of gravity, but this can be difficult since the lapse is frequently followed by a quick compensatory antigravity movement to restore limb position. Asterixis is usually irregular, but when it comes rapidly there may be the appearance of tremor.

In clinical practice, it is of course valuable to couple EMG studies with either kinesiologic or EEG observations or both. Nevertheless, the simple application of EMG can be extremely helpful as a first step.

3. Kinesiology, accelerometry

Kinesiology is the study of body movement and includes kinematics, the measurement of movement, and kinetics, the measurement of forces that produce a movement. Kinematics is frequently combined with EMG in the clinical neurophysiological investigation of movement and movement disorders. There are multiple methods and devices for the measurement of kinematics, and they need to be used carefully to obtain accurate information.

The human body consists of multiple segments that are linked by joints. The body segments vary in size, shape and deformability, and the joints vary in their rotational degrees of freedom. Muscles acting about each joint produce moments of force that rotate one segment relative to another. Therefore, a point on the body (e.g., the total-body center of mass) may exhibit linear or curvilinear motion, but this is always the result of linked body segments that rotate with respect to each other. This is analogous to the linear motion of an automobile, produced by wheel rotation. The kinematics and kinetics of multi-joint 3-dimensional human motion are too complex be comprehensively characterized with a single motion transducer such as a triaxial (3-dimensional) accelerometer, but a single transducer or inertial measurement unit can often produce useful and sufficient information if properly deployed.

Three types of accelerometer are used in human applications: piezoresistive, piezoelectric and capacitance devices. All three types contain a small seismic mass attached to an elastic element, and the elastic element is stretched or compressed in proportion to acceleration. Acceleration is thereby determined using Newton’s law of mass acceleration (force = mass • acceleration) and Hooke’s law of spring action (force = spring constant • change

in length of a spring). Very small, inexpensive accelerometers are manufactured using microelectromechanical systems (MEMS) technology, and they are used in a variety of electronic devices, including smart phones, smart watches and activity monitors, all of which have been used to measure physiologic and pathologic movements (Elble et al., 2016).

Accelerometers have been used in the study of physiologic and pathologic tremor for more than 60 years. However, their limitations are often unappreciated or ignored. Perhaps the two most important limitations are 1) nearly all commercially available accelerometers detect linear acceleration and 2) they are influenced by earth's gravity $g = 9.81$ m/s^2. Therefore, if an accelerometer rotates in space, the axes of the accelerometer will rotate with respect to earth's gravity, producing fluctuating gravitational artifact at the frequency of rotation. This artifact cannot be removed with filtering, so it will confound the desired measurement of inertial acceleration. A linear accelerometer spinning in space in one location (i.e., rotating on the axis of rotation) will produce an output that fluctuates between $\pm 1g$ and will detect no inertial acceleration despite the forces needed to rotate the device in space. A linear accelerometer detects angular (rotational) inertial acceleration only to the extent that the axes of sensitivity are located some distance L from the axis of rotation (Figure 4). The output of an accelerometer is linearly proportional to L, and inconsistent placement of an accelerometer will therefore produce inconsistent measurements.

A single accelerometer, even one with three orthogonal axes of sensitivity (triaxial accelerometers), can produce only a very limited assessment of multi-joint limb motion. An accelerometer mounted on the hand will have an instantaneous axis of rotation that is proximal to the wrist if rotation also occurs at the elbow or shoulder, and the location of the instantaneous axis of rotation will vary to the extent that rotation varies among the wrist, elbow and shoulder. This variation in the instantaneous axis of rotation will produce proportional variation in the amplitude of acceleration detected by the accelerometer, and it may also affect the frequency content of the recordings. Consequently, linear accelerometers are suitable for measuring tremor amplitude only when motion is restricted to one joint, motion is primarily in one direction, and the transducer is mounted in a consistent location (Elble, 2005, Elble et al., 2016). These three requirements are nearly impossible to achieve in human applications. Angular rotation can be measured with multiple accelerometers mounted on the same body segment (Figure 4), but the problem with this approach is that the transducers must be strategically mounted with precise orientation of their axes (Elble, 2005). Similarly, tremor frequency is measured most reliably when motion is restricted to a single joint and a standardized task (Longardner et al., 2019, Vial et al., 2019).

Most three-dimensional accelerometers are now packaged in small, inexpensive inertial measurement units (IMUs) that also contain three-dimensional gyroscopes and frequently contain a triaxial magnetometer. The gyroscopes measure angular velocity of the body segment, to which the gyroscope is attached. Gravitational artifact is not an issue with gyroscopic transducers, but the relative rotations of multiple joints can make interpretation difficult. For example, consider a gyroscope on the hand, with the upper limb fully extended horizontally. A 30-degree oscillation at the wrist will displace the hand in space far less than a 30-degree oscillation at the shoulder because the arc length of motion of any point on the hand is proportional to the distance from that point to the axis of rotation (Figure 4).

Therefore, when assessing tremor amplitude, it is preferable to restrict motion to one joint if possible because it is impossible to know or control the instantaneous axis of rotation when multiple joints are involved in a movement. Furthermore, the frequency of rotation may differ among joints, and a single IMU will detect these frequencies but cannot locate their origins.

The limitations of accelerometry versus gyroscopy are illustrated in the measurement of head tremor in patients with essential tremor and cervical dystonia (Elble et al., 2017). An IMU mounted at the vertex of the head is capable of recording head motion in three-dimensional space. Head motion is primarily rotational, and the instantaneous axis of rotation will usually vary over time because head tremor is usually multi-directional. For tremor in the horizontal plane, the instantaneous axis of rotation will be close to an IMU mounted at the vertex of the head. Accelerometers therefore give misleadingly small and variable estimates of tremor amplitude (Figure 5). By contrast, a three-dimensional gyroscope produces valid estimates of tremor amplitude that correlate very strongly with clinical ratings (Elble et al., 2017).

In some applications, the occurrence of an abnormal movement, rather than its amplitude, may be the desired measure. IMUs, particularly accelerometers, are extremely sensitive to movement, and frequency-domain and time-domain statistical features of a movement are useful in identifying the type of movement (e.g., normal walking, chorea, tremor) and in answering the binary question “present or absent”. For example, the frequency content of most normal movements is primarily in the range of 0-3 Hz, and all tremors except myorhythmias have frequencies >3 Hz. Furthermore, tremor, by definition, is rhythmic and oscillatory (Bhatia et al., 2018). Therefore, tremor-detection algorithms are easy to develop using methods of spectral analysis to detect rhythmic motion at a frequency >3 Hz. These tremor-detection algorithms have good sensitivity and specificity for pathologic tremor (Thorp et al., 2018), and the percentage of awake time with tremor correlates strongly with clinical ratings of rest tremor in Parkinson disease (Hoff et al., 2001). Other abnormal movements are not rhythmic and have frequency content and other kinematic features that overlap with those of normal voluntary movement. Consequently, mathematical algorithms for identifying arrhythmic movements (e.g., chorea, dystonia, myoclonus) must utilize additional frequency-domain and time-domain methods of signal (time series) analysis to answer the binary question “present or absent”.

Algorithms for detecting abnormal movements typically combine frequency- and time-domain signal characteristics (statistics) with machine learning (Bennasar et al., 2018, Lonini et al., 2018). These algorithms are developed empirically, using large volumes of clinical data, to distinguish abnormal involuntary movements from normal movements and to distinguish among the various types of abnormal movements. Continuous recordings with wearable IMUs can identify "on" time, "off" time, and time with dyskinesia in Parkinson disease (Pfister et al., 2020). Optimum placement and optimum number of IMUs appear to differ among the various disturbances of motion (bradykinesia, freezing, rest tremor, dyskinesia) in Parkinson disease (Thorp et al., 2018). These factors, the influence of activities of daily living, within-subjects variability, and between-subjects variability are continuing challenges in this field (Thorp et al., 2018).

Multiple strategically mounted IMUs are needed for a detailed kinematic analysis of movements involving multiple body segments. This is illustrated in relatively simple studies of elbow rotation (El-Gohary et al., 2015) and knee rotation (Favre et al., 2008, Jakob et al., 2013, Seel et al., 2014). The computational analysis of IMU recordings in 3-dimensional motion capture is not trivial, but commercial software (www.xsens.com/motion-capture) and freeware (simtk.org/projects/opensim) are available for this purpose (Tagliapietra et al., 2018). Motion capture with IMUs is accomplished by "fusing" the three-dimensional accelerometer, gyroscope and sometimes magnetometer recordings (depending on the magnitude of environmental ferromagnetic interference) with a kinematic model of the body segments using a mathematical algorithm (e.g., extended Kalman filter) to determine the orientation of each IMU with respect to a global coordinate system that is based on earth's gravity and sometimes magnetic North (Jakob et al., 2013, Lebel et al., 2013). The accuracy of this approach varies with the design of the IMU, number of IMUs, velocity of motion, duration of motion, and environmental ferromagnetic interference (Lebel et al., 2013). Three-dimensional camera-based motion capture systems are still the gold standard particularly for gait analysis (see next section), but these systems are laboratory-based and expensive (Jakob et al., 2013). There are a variety of systems with active and passive markers positioned on body parts, and newer systems are being developed that are markerless (Colyer et al., 2018, Menolotto et al., 2020)

Most applications do not require a comprehensive kinematic analysis of motion. For example, single IMUs can be used to obtain representative performance measures such as step count, arm swing, turning, and postural sway as described in the next section (Case et al., 2015, Mancini et al., 2016b). Furthermore, there are alternatives to IMUs, depending on the desired clinical application. Goniometers are being used to assess tremor in the shoulder, elbow and wrist to guide clinicians in the administration of botulinum toxin, tailored to the distribution of each patient's tremor (Samotus et al., 2018). Three-dimensional camera-based motion capture systems can accurately record limb trajectories, as in a reaching task (Deuschl et al., 2000). Three-dimensional ultrasound (Pedrosa et al., 2013) and electromagnetic systems (Matsumoto et al., 2001) have also been used for this purpose.

In summary, wearable motion transducers and recording systems are becoming increasingly portable, accurate and affordable. The effective use of these devices requires a careful consideration of the objectives and complexities of the desired application and the limitations of the available devices. For example, a detailed kinematic analysis of the upper limb is necessary to study joint interaction torques and rotations underlying decomposition of movement during a reaching task in ataxia (Bastian et al., 1996), but it is not needed to assess the functional impact of tremor or dysmetria of the hand (Bastian et al., 2000, Deuschl et al., 2000). Furthermore, clinical performance assessed with a clinical rating scale can be as sensitive as an IMU to clinically important change because the advantages of transducers (sensitivity and precision) are largely mitigated by test-retest (within-subjects) variability in performance (Elble et al., 2016). Clinicians must therefore choose their tools wisely when assessing movement disorders.

4. Balance and Gait Analysis

Balance control has the goal of maintaining postural equilibrium, that is control of the body center of mass over its base of support. Gait control has the goal of efficiently and effectively moving the body in space using the legs. However, balance and gait each consist of several, separate domains (Figs. 6 and 7) that are affected independently by different neurological disorders and therapeutic interventions and, thus, are likely controlled by different brain circuity. Thus, a comprehensive assessment of balance or gait requires testing control of each domain because a disorder within each domain has different functional and clinical implications.

Here, we describe 3 general approaches to assess each balance and gait domain: 1) clinical assessments by a neurologist or physical therapist without technology; 2) clinical neurophysiology assessment with laboratory equipment and expert analysis and interpretation of results, and 3) upcoming clinical neurophysiological assessment using less expensive, wearable technologies with automatic (or semi-automatic) algorithms to derive outcomes for prescribed tasks and free-living mobility. Figure 6 summarizes the 3 types of assessments for 6 Balance Domains: Postural Alignment (posture), Subjective Vertical, Limits of Stability, Postural Sway, Automatic Postural Responses, and Anticipatory Postural Adjustments. Five of the 6 balance domains are assessed in a clinical balance test called the “Balance Evaluation Systems Test” (BESTest) as indicated by the asterisks (Horak et al., 2009, Mancini et al., 2010). Figure 7 summarizes 6 gait domains: Pace, Temporal, Variability, Asymmetry, Stability, and Transitions (e.g.; Turning and Sit-to-stand) that have been identified using Factor Analysis or Principal Component Analysis (Lord et al., 2012, Horak et al., 2016).

Balance Domains

Posture or Postural Alignment—is the relationship of body segment positions to one another and to gravity, the base of support and surrounding environment (Bullock-Saxton, 1993). Optimal postural alignment is a prerequisite for optimal functional movements. Appropriate postural alignment allows stability (balance) as well as body orientation in space by integrating visual, vestibular and proprioceptive inputs to make postural adjustments (Carpenter et al., 2004). A tilted or inaccurate internal representation of postural or visual verticality (see Subjective Vertical, below) could result in abnormal posture that is not aligned with gravity (Horak and Macpherson, 2011, Bronstein et al., 2013). Examples of postural misalignment are often seen in people with Parkinson’s disease (PD), who present a characteristic flexed posture as well as, up to one third who have deformities of their neck or trunk such as camptocormia (forward bent trunk), anterocollis (flexed neck), Pisa syndrome (lateral lean of trunk) or scoliosis (Ashour et al., 2006, Benatru et al., 2008). Clinicians can measure, in degrees, postural alignment between different body segments with goniometers and alignment respect to the vertical of the whole body with posture grids. Standard Clinical Neurophysiology uses motion analysis kinematics to accurately quantify postural alignment during static quiet standing (where the participant is asked to stand still from a minimum of 30s up to a couple of minutes) or during walking. Reflective markers are placed on many body segments and a biomechanical model allows the calculation of displacement and

orientation of each body segment, as well as estimates of position of the body center of mass (CoM). More recently, accelerometers or Inertial Measurement Units (IMUs) have been used to calculate the inclination of a body segment from gravity and the change in inclination over time (Vaugoyeau et al., 2007, Carpenter et al., 2011).

Subjective Vertical—is the perception of upright (gravity) that arises from an internal representation based on the integration of somatosensory, vestibular and visual information, and prior experience (Bisdorff et al., 1996, Dieterich et al., 2019). Subjective *visual* vertical is thought to be independently controlled from subjective *postural* vertical since patients usually have one or the other affected (Dieterich et al., 2019). Subjective visual vertical measures the accuracy of aligning a visual line to gravitational vertical when other visual cues are not available (e.g., in the dark). Visual vertical is often evaluated by asking subjects to align a line across the diameter of a large to their perceived 'vertical' with an inclinometer (as from an application in a smart phone) on the bottom of the bucket to indicate degrees away from gravitational vertical. Laboratories can more accurately measure subjective vertical with a remote-control laser line in a dark room. In contrast to visual vertical, postural (somatosensory) vertical is measured by asking the patient to indicate perceived vertical, such as with a light, hand-held rod, while they are tilted while standing or sitting on a tilt board. An accelerometer on the rod can indicate tilt away from gravitational vertical. Healthy adults showing normal visual vertical are accurate <±1 degree and postural vertical < ±2 degrees. Patients with unilateral vestibular loss often show abnormal visual vertical, whereas patients with right-sided stroke (left brain affected) or with progressive supranuclear palsy (PSP) can show abnormal postural vertical (Dale et al., 2017). An altered visual or postural verticality sense may affect posture as well as balance, resulting in being more vulnerable to falls(Vaugoyeau et al., 2007, Carpenter et al., 2011).

Postural Sway—refers to the horizontal (antero-posterior and medio-lateral) movements around the body CoM during quiet standing, (i.e., static posturography) (Bloem et al., 2003). The ability to maintain postural equilibrium in static postures relies on the ability of the central nervous system to control the body's CoM so that it remains within safe boundaries above the base of support (Winter, 1995, Winter, 2009). Postural sway during quiet standing is commonly quantified by the motion of the Center of Pressure (CoP), namely the point of application of the ground reaction force vector under the feet (Morasso et al., 1999), using a force plate. Clinicians judge sway area using subjective assessment and with stopwatches to time how many seconds a person can hold a particular stance (i.e., feet together, eyes closed etc.).

CoP movements are closely related to the Center of Mass (CoM) movements during quiet standing. Force plates act as dynamometers using mechano-electrical force transducers (strain gages or piezoelectric crystals) and record the ground-reaction forces between the body and ground, thus allowing the calculation of the CoP (Winter, 1995, Chiari, 2009). In fact, even small deviations from an upright body position result in a gravity-induced torque acting on the body, causing it to accelerate further away from the upright position. As a consequence, several muscles activate to oppose the destabilizing torques due to gravity making standing still a very active process, where visual, somatosensory, and vestibular need

to be working together. When a sensory input is distorted or removed, e.g., when vision is not available or the visual surround is moving sway will increase. Impairments in sensory, motor, or central nervous function, caused by the natural aging process or pathology, will reflect in changes in maintaining stability during postural sway. Thus, measures of the CoP during sway are of critical importance to unravel neural mechanisms of postural control (Winter, 2009). In addition, CoP analysis may serve as an objective way to assess severity of postural instability in people with neurological diseases (Maurer et al., 2000, Visser et al., 2008).

Several methods exist to characterize postural sway and one of the most common is considering the signal stationary and describing it in the time and frequency domains (Chiari, 2009). Sway has been shown to consist of three different components, area, velocity and frequency. Figure 8 shows the CoP trajectories in the horizontal plane (called a stabilogram) of a representative healthy control and a representative individual with Parkinson's disease Off and On dopaminergic treatment. People with Parkinson's disease often show impaired postural stability, characterized by larger, faster and higher frequency sway in both the medio-lateral and antero-posterior directions compared to age-matched healthy controls. In addition, while levodopa replacement helps certain aspects of mobility, such as gait speed and APAs (below), it does not improve postural sway (Rocchi et al., 2002, Schoneburg et al., 2013). In fact, postural sway area may increase when individuals with PD are On levodopa for many reasons, such as reduced rigidity, increased dyskinesia, and interference with control of standing balance (Curtze et al., 2015).

Over the past 20 years, several studies shown the validity and sensitivity of measuring postural sway with wearable sensors, such as a single IMU (e.g., a Smart phone) attached to the low back, compared to a force plate (Mayagoitia et al., 2002, Moe-Nilssen et al., 2002, Mancini et al., 2011). Inertial sensors provide a robust and valid approach to characterizing postural sway, although some algorithms use linear accelerometers, other use angular velocity to calculate changes in rotation of the trunk, and others use both.

Limits of Stability—is how far a subject can lean their body CoM over their base of support without external support or taking a step (Schieppati et al., 1994). To assess limits of stability, clinicians ask a standing patient to reach forward (or backwards or sideways) as far as they can (Functional Reach Test) next to a tape measure on the wall (Duncan et al., 1992). However, subjects can reach without moving their body CoM so the Functional Reach Test results does not always relate well to displacement of the CoP on a force plate. Limits of stability can be measured while standing on a force plate as the maximum CoP movement and velocity while attempting to lean (Schieppati et al., 1994). Motion analysis can be used to measure the kinematic strategy used to achieve the maximum limits of stability (Mancini et al., 2008). Limits of stability are particularly impaired in the forward direction in people with Parkinson's disease compared to age-matched healthy controls, while the backward limits of stability are similar among people with PD and age-matched healthy controls (Mancini et al., 2008). While levodopa treatment helps increase forward limits of stability, it does not restore it to a normal range (Mancini et al., 2008). Clinicians can now use wearable sensors on the low back (near the center of mass) while subjects lean to measure limits of stability to measure maximum displacement of the trunk.

Automatic Postural Responses (APRs)—are the automatically-triggered muscle responses to sudden, external disturbances to body equilibrium (Horak and Macpherson, 1996). The first muscle bursts activated when a standing human is pushed forwards or backwards are ankle muscles at 90-120 ms, although stepping responses often have even longer latencies. Postural muscle responses are activated in groups, called *synergies*, that receive a common command signal dependent upon the direction and speed of the disturbance (Ting et al., 2007). For example, when forward sway is induced by an external perturbation, the distal-to-proximal muscle synergy results in an *ankle strategy* that restores balance primarily by rotating the body about the ankle joints (Horak and Nashner, 1986). However, when forward sway is induced when standing across a narrow beam, such that surface forces cannot restore equilibrium, a hip and trunk muscle synergy results in a *hip strategy* to restore body center of mass by bending at the hip joints and counter-rotating at the ankle joints (Horak and Nashner, 1986). Postural responses are influenced by recent experience, so they adapt gradually to a sudden change in biomechanical conditions, such as from a flat, firm surface to a narrow beam or from standing to sitting (Horak et al., 1992). Postural responses can also improve with practice (Dijkstra et al., 2015, Peterson et al., 2016). However, patients with Parkinson's disease demonstrate mixed ankle and hip strategies that do not quickly adapt to new biomechanical conditions and slower improvement of postural responses with practice (Horak et al., 1992, Peterson et al., 2016).

Clinician generally assess APRs using the "Pull test" or the "Push and Release test" (Jacobs et al., 2006). Clinicians assess the ability to recover equilibrium by taking a single step after pulling backward on the shoulders in the Pull test. Perturbations to postural equilibrium are induced via sudden release of isometric muscle forces by the patient against the clinician's hands on the shoulders or hips in the Push and Release test. The Push and Release test allows evaluation of both feet-in-place responses, such as the ankle strategy, as well as stepping responses.

APRs can be evaluated more precisely in the laboratory by providing velocity-, amplitude- and direction-controlled perturbations to equilibrium, such as sudden translations or rotations of the surface or by pulling on a harness or releasing a harness that a subject is leaning against (Mille et al., 2003). Surface EMG, surface reactive forces and whole-body kinematic responses are then characterized. For example, forward translation of the surface upon which a subject stands results in backward body CoM tilt which must be overcome by activating tibialis anterior, quadriceps and abdominal muscles, resulting in a torque on the surface that can be characterized as the latency, peak, rate of rise and area of the CoP displacement (Fig. 9A). Although people with PD have normal latencies to the onset of postural responses, their peak, rate of rise and area of CoP response to external displacements are small and are not improved with levodopa therapy (Fig. 9A). Recently, patterns of multiple muscle surface EMG activation have been characterized as postural synergies in response to external displacements (Chvatal et al., 2013, Sawers et al., 2017). Small studies have shown that people with PD have abnormal postural synergy structure that is not improved by levodopa nor DBS (Mileti et al., 2020). Wearable sensors can also be used to quantify APRs during the Pull test or the Push and Release test. Measures like

postural response latencies, compensatory step length and step velocity, and time to recover equilibrium may be useful objective measures for clinical researchers(Craig et al., 2017).

Anticipatory Postural Adjustments (APAs)—are postural muscle activations that occur in anticipation of voluntary movements to prevent destabilization of postural orientation and equilibrium. APAs are specific to biomechanical conditions. For example, when a standing subject rapidly lifts their arms or pulls on a handle, leg muscles are activated prior to arm muscles (Horak et al., 1984). However, when the subject performs the same pull with their body is supported, no anticipatory leg muscle activity occurs and arm muscle activation occurs earlier (Cordo et al., 1982). APAs are also critical for step initiation as they accelerate the body center of mass forward and laterally to unweight the leg about to step. This anticipatory postural adjustment is independent of locomotor control. Clinicians and physical therapists cannot easily assess APAs but they can infer a problem if their patients have difficulty with postural transitions, such as step initiation, stand on one foot or the sit-to-stand task.

In the laboratory, APAs are assessed primarily as changes in center of pressure under the feet prior to a voluntary movement and by the muscle synergies responsible. For example, APAs associated with step initiation are initiated by hip abductor muscles, such as tensor fasciae latae, in the leg about to step and bilateral tibialis anterior muscle activation. The size of an APA prior to step initiation can be measured as the peak lateral (and anterior) displacement of the CoP (Fig. 9B). APAs have been shown to be weak or absent in people with PD and improved by dopamine replacement therapy (Burleigh-Jacobs et al., 1997) (Fig. 9B). Recently, APAs associated with step initiation have been captured with an inertial sensor placed on the lumbar spine of subjects, which makes it possible for clinicians to quantify the amplitude of APAs (Mancini et al., 2016a). Acceleration of the sensor towards the support leg and forward coincides with displacement of the center of pressure under the feet towards the stepping leg and backward prior to step initiation (Mancini et al., 2016a).

Gait Domains

Gait temporal and spatial measures all are defined and averaged across gait cycles. A gait cycle is defined as the interval of time between successive heel strikes at which the heel of the same foot strikes the ground (Fig. 5 shows the cycle of the right leg). The gait cycle includes a stance phase, during which the foot is in contact with the ground (60% to 70% of the cycle duration), and a swing time (30% to 40% of the cycle duration), which begins when the toes leave the ground and, by definition, is equal in time to the single support time of the other leg. About 20-25% of the gait cycle, both feet are in contact with the ground (double-support). The double support time can be increased in patients with postural instability, for example with aging or neurological conditions.

Classic gait spatio-temporal parameters, such as step length (distance leg travels between right and left heel strikes) or stride length (distance leg travels between one leg heel strikes), are calculated with respect to each gait cycle and averaged across gait cycles. Gait has been shown to consist of several, separate, relatively uncorrelated, components such as pace, timing, variability, asymmetry, postural stability, and turning (Lord et al., 2012).

Gait Pace—represents measures related to the speed of locomotion, such as stride velocity (or gait speed), stride length, and cadence (steps per minute). Energization of gait, as well as voluntary movement in general, is thought to be driven from the basal ganglia via the motor cortex to brainstem locomotor centers so is affected by Parkinsonian disorders (Mancini et al., 2020). However, gait also slows to compensate for imbalance, asymmetry, temporal and variability impairments that disrupt locomotion so can be a sensitive predictor of future fall risk and even mortality in the elderly (Hausdorff, 2007). Gait pace is most commonly measured as 'gait speed' in the clinic using a stopwatch or distance walked over a fixed time (Fig. 10). Most clinical walking tasks are performed at patient's normal pace, although some walks, such as the 25-foot walk and the 6-minute walk tests, are performed with instructions to walk as fast or as far as possible, respectively. Characteristics of gait quality can be derived from sophisticated and well-equipped gait analysis laboratories. These laboratories include motion analysis systems, force-plates, and wireless surface EMGs to characterize kinematics (joints motion) and kinetics (forces that act across the joints) of gait as well as muscle activity during walking. Together, they provide a comprehensive picture of the various factors contributing to gait disorders. Recently, clinical trials and clinical practice take advantage of wearable technology, in the form of inertial sensors, to quantify gait pace metrics more quickly and with less expensive equipment compared to a fully equipped gait laboratory. Studies have shown that inertial sensors on the feet produce the most accurate measures of gait speed, followed by sensors on the ankles and then waist (Hsu et al., 2018). Since prescribed walking tasks in the laboratory may not reflect how people walk in daily life, when their attention is diverted to other tasks, it is increasingly popular to add a cognitive, "dual task" while walking (Hyndman et al., 2004, Hausdorff et al., 2008). This cognitive-gait interference is calculated as the percent change in gait parameters, such as slowing of velocity or shortening of step length, compared to the same parameters without the dual-task. The amount of change is thought to be related to how much control of gait requires cortical attention, or lacks automaticity (Clark, 2015). In fact, dual-task cost can be especially high in patients with neurological disorders who are at a high risk for falls (Hausdorff et al., 2008).

Gait Timing, Variability and Asymmetry—refers to 3 different domains of gait (Lord et al., 2012). *Temporal* aspects of gait, such as double- and single-support time arise from crossed connections between spinal, brainstem and cortical locomotor centers and can reflect compensation for postural instability (e.g.; by reducing % of time spent on one foot and increasing % of time spent on two feet). Thus, increased double support time has be related to fall risk (Kwon et al., 2018). *Variability* of gait measures, using standard deviations, coefficient of variation, etc. are the most sensitive gait measures in patients with cerebellar disorders (Hausdorff, 2004, 2009). Consistency of gait is thought to be due to automatic spinal locomotor control but gait becomes more variable with more corticospinal control of the locomotor centers, indicating it is less automatic (Maidan et al., 2016). *Asymmetry* of right-left leg movements (stride time or length) can reflect either central nervous system lateralized lesion (i.e., stroke) or biomechanical impairments (i.e., leg joint or muscle). Clinical gait assessments cannot distinguish among these 3 domains of gait control. Clinical rating scales for gait such as the Tinetti Performance Oriented Mobility Assessment (Tinetti, 1986) and the Gillette Gait Index attempt to use ratings of

task accomplishment or visual qualitative assessment of kinematic parameters (Wren et al., 2007). Gait laboratories generally use a combination of whole-body kinematics with motion analysis as well as ground reaction forces from force plates for a single step (located in the center of the motion analysis calibrated space) to quantify leg joint displacements, power of push-off, and the temporal, variability and asymmetry domains of gait. Alternatively, good measures of foot fall during gait can be obtained with gait pressure mats, although upper body motions and turning are generally left out. Wearable sensors have been extensively used to automatically quantify many gait metrics, with the most accurate metrics from placement on the feet, then ankles, then low back compared to gold-standard motion analysis or pressure sensor walkways (Storm et al., 2016). Body-worn inertial sensors allow for much longer walking task across a variety of environments, including continuously during daily life (Horak et al., 2015). Gait during daily life has been shown to be slower and more variable than gait measured in a laboratory test (Hillel et al., 2019). Daily life gait also consists of over 85% of gait bouts lasting less than 10 seconds and gait speed is slower, the shorter the bout (Shah et al., 2020a). Recent studies suggest that quantifying gait quality during daily life is more sensitive and specific than the same gait measures derived from a gait tasks in a laboratory.

Postural stability—during walking involves controlling the CoM of the upper body over the moving legs, especially in the lateral direction. Excessive lateral displacement of the trunk and excessive lateral and externally rotated foot placement and their increased variabilities are signs of postural instability during locomotion (Dean et al., 2007). Patients with abnormal postural stability during gait may exhibit normal automatic and anticipatory postural adjustments, normal postural sway in stance under different sensory conditions, and normal orientation to vertical, suggesting that postural control and gait have different nervous system circuits. Several clinical rating scales (such as the Dynamic Gait Index) attempt to assess postural stability during gait by adding postural challenges to walking, such as obstacle clearance, changes gait speed, rotating the head, and adding a cognitive task. Most clinical gait scales either rate how much assistance is needed to walk or what type of gait is possible (jumping, running, etc.). No clinical tests specifically evaluate trunk stability or foot placement to rate postural stability during gait, although the BESTest and MiniBEST evaluates trunk motion and veering of locomotion during challenges such as head rotations. Motion analysis or wearable sensors on the trunk can be used to estimate postural stability during walking by quantifying the range of trunk motion in each gait cycle and by measuring double support time and variability of foot heading. Stability during gait can also be assessed via local dynamic stability (LDS) measures of the trunk acceleration while walking (Ihlen et al., 2012). Phase-dependent LDS is an indicator of the rate at which local perturbations are attenuated during specific phases of the gait cycle (Ihlen et al., 2012). Impaired phase-dependent LDS during weight transfer, but not other phases, is found in people with neurological disorders compared to their healthy peers (Fino et al., 2018) and is a sensitive discriminatory measure between elderly fallers and non-fallers during daily life (Ihlen et al., 2016).

Turning—involves a change in direction of forward progression. The ability to modify the direction of locomotion is fundamental yet a complex component of walking behavior.

Turning requires the central nervous system to coordinate body re-orientation towards a new travel direction, while continuing with the on-going step cycle, and at the same time maintaining postural stability in the medial-lateral plane (Patla et al., 1999). Normally, gaze rotation initiates the turn and occurs approximately 200 ms before the start of the turn (Courtine et al., 2003, Hicheur et al., 2005). After the head, then the trunk, later the pelvis and feet rotate to the inner side of the turning cycle and the center of mass (CoM) deviates to the same side (Crenna et al., 2007). During turning, velocity decreases and stride width increases to improve stability of body weight during trunk rotation and lateral translation, compared to straight gait. Turning is essential to functional mobility in daily life, in fact, the majority of activities during daily life require 3-4 turns and over 50% of daily steps are turning steps (Glaister et al., 2007).

Clinical assessment of turning is largely based on counting the steps and recording the time to complete a 360-degree turn-in-place with a stopwatch. Although increased turning duration reflects typically reflects turning impairments, other aspects of turning not assessed with this approach, such as stability during turning, inter-limb coordination, and smoothness. In fact, when some neurological patients turn faster, they are more unstable and likely to fall. Motion analysis and surface EMGs can be used to quantify stability and multi-segment coordination during turning. Turning impairments are common in people with PD (Stack et al., 2008) from early in the diagnosis, and negatively affect functional independence. In fact, impairments during turning difficulties have recently been shown to be a major risk factor for falls, institutionalization and death in PD (Morris et al., 2001). Turning maybe more prone to impairments compared to straight-ahead gait because of its complex nature. In fact, coupling between balance and gait and modification of locomotor patterns during turning likely require frontal lobe cognitive and executive function (Herman et al., 2011). Gait characteristics change a few steps before and after a turn so steady-state, straight-ahead gait should consider these steps separately when calculating gait characteristics.

Physical activity (accelerometry).—Physical activity, as opposed to sedentary time, is a key component of health, well-being, and mental health (Taraldsen et al., 2012). The most common measures of physical activity use light-weight, accelerometer-based wearable sensors that continuously record motion over several days (Taraldsen et al., 2012). Quantitative evaluation is possible using light-weight, motion-sensing accelerometer-based devices that continuously record positional change and motion over days (Taraldsen et al., 2012). Outcomes have typically been derived from activity counts and activity recognition (sedentary, moderate and vigorous levels of activity), but lately have been described in terms of activity pattern and compositional data analysis, such as time spent standing versus lying, number of sit-to-stands and number of stairs up and down, as well (Chastin et al., 2010, Lord et al., 2011). However, the information is often limited to the overall *quantity of activity*, or gross measures that may not be sensitive to subtle mobility changes.

Daily Life Mobility Monitoring.—In contrast to the quantity of physical activity with accelerometry, the *quality of activity*, specifically quality of walking and postural transitions (sit-to-stand, turning) can also be measured with inertial sensors during daily life (Horak et al., 2015, Del Din et al., 2016). Gait and turning measures during daily life (as also

described in prescribed walking tasks) are sensitive and specific to neurological disease (Horak et al., 2015, Del Din et al., 2016, Hillel et al., 2019, Shah et al., 2020a, Shah et al., 2020b) and predict falls in the elderly (van Schooten et al., 2016). It is known that mobility assessment in the laboratory or clinic reflects more the capacity of individuals, i.e. what an individual can do, rather that mobility function during daily life. This is particularly observed in people with PD, in fact, walking performance assessed in the clinic is far superior than the motor performance reported during daily life by a caregiver or spouse. There are many potential benefits of digital biomarkers of mobility in unsupervised settings for clinical care as well as for digital endpoints in future intervention trials (Warmerdam et al., 2020). In fact, daily life measures of gait and balance have the potential to revolutionize health care (Warmerdam et al., 2020). However, this field is very young, and although such technologies are now widely available in consumer devices such as smart phone applications and exercise devices, care should be used as many devices and algorithms have not undergone validation, particularly for patient populations. In addition, harmonization of protocols and devices has not been established (Warmerdam et al., 2020).

5. EEG, MEG, ECoG, SEPs, and Correlations with EMG

The electroencephalogram (EEG) and magnetoencephalogram (MEG) have been effectively applied to the elucidation of the central control mechanism of voluntary movement and of the pathophysiology underlying the generation of various involuntary movements (Shibasaki, 2012). The correlation of cortical activities with movements can be studied noninvasively by the simultaneous recording of EEG and/or MEG with the electromyographic (EMG) correlates of movements. Recording of cortical activities directly from the epicortical electrodes (electrocorticogram, ECoG) as a part of the presurgical evaluation of patients with medically intractable epilepsy have provided supportive evidence for the findings obtained by those noninvasive techniques. In special cases of involuntary movements like myoclonus which are characterized by over-excitability of the primary somatosensory cortex (S1) and the primary motor cortex (M1), cortical responses to various stimuli can be studied by using evoked responses, especially the somatosensory evoked potentials (SEPs) (Shibasaki et al., 2005).

EEG, MEG and EcoG

It is well established that-both EEG and MEG reflect the electrical activity generated in the apical dendrites of large pyramidal neurons in the cerebral cortex (Shibasaki et al., 2007). When an apical dendrite is activated at a specific site in response to an excitatory synaptic input, the extracellular current flows from other sites of that apical dendrite (source) into the activated (depolarized) site (sink) (Fig. 11). For example, if an apical dendrite is activated near the cell body, then the extracellular current flows from the tip of the apical dendrite into its deep layer, thus producing a surface-positive, depth-negative electrical field distribution with respect to the cortical surface. EEG is the summation of these electrical fields generated from many neurons and recorded from the head surface. Intracellularly, the electrical current flows from the activated (depolarized) site to other sites of that apical dendrite. If we place the right thumb along the direction of this intracellular current flow, magnetic flow is generated in the direction of other fingers of the right hand surrounding the

current flow or the apical dendrite (Fig. 12). This is the reason that to the magnetic field, the MEG sensor must be placed tangentially with respect to the apical dendrite.

Cortical activity associated with involuntary movements

Involuntary movements vary widely from a simple muscle contraction like cortical myoclonus to complex movements like chorea, dyskinesia and athetosis. Among these involuntary movements, abnormalities of the sensorimotor cortex (S1-M1) have been identified in cortical myoclonus, tremor and focal dystonia (Shibasaki, 2012, Avanzini et al., 2016, Chen et al., 2020).

Cortical myoclonus as seen in patients with progressive myoclonus epilepsy is-often preceded by a spike on EEG. With a conventional EEG–EMG polygraph, however, it is difficult to study the temporal and spatial relationship between the EEG spike and the myoclonus precisely (Fig. 12). In this case, the technique of back averaging EEG or MEG with respect to the myoclonus onset may be effective (jerk-locked back averaging) (Shibasaki et al., 1975, Shibasaki et al., 2005) (Figs. 13, 14). Technical details for performing back averaging are published (Merchant et al., 2020, Vial et al., 2020).

Cortical myoclonus is characterized electrophysiologically by a preceding spike arising from the somatotopically corresponding part of M1, a pathologically enhanced somatosensory evoked potential (giant SEP), and an exaggerated long latency, long loop reflex called ‘C reflex’ (C for cortex which was assumed to be the site of mediation of the reflex) by Sutton and Mayer (Sutton et al., 1974) (Fig. 15). The same electrophysiological findings are demonstrated also in patients with negative myoclonus of cortical origin (cortical reflex negative myoclonus) (Shibasaki et al., 1994). Application of MEG provided these physiological abnormalities with better spatial resolution (Uesaka et al., 1996, Mima et al., 1998, Anzellotti et al., 2016) (Fig. 16).

The C reflex has been shown to be caused by pathological enhancement of a component (called LLR2, M2 or V2) of the long loop reflex, which is observed during sustained contraction of the corresponding muscle in normal subjects (Deuschl et al., 1990). Based on noninvasive, electrophysiological studies including MEG, there is now evidence that the mechanism of C reflex is transcortical via S1-M1 (Shibasaki et al., 2005). Hitomi et al. (Hitomi et al., 2006) by epicortical recording in a patient with focal cortical reflex myoclonus as a part of presurgical evaluation, demonstrated temporal pattern of giant SEPs in the somatosensory area (Fig. 17). In response to tibial nerve stimulation, a giant SEP was first seen at the foot area of S1, and 5 ms later it was followed by a giant potential at the foot area of M1.

Cortical activities associated with voluntary movements

Kornhuber and Deecke (Kornhuber et al., 1965) first recorded EEG activity preceding volitional movement in humans (Fig. 18). Cortical activity recorded by EEG or MEG in association with voluntary movements have been mainly applied for research purposes. Their clinical application is limited partly because recording of the movement-related cortical activity is often complicated by technical difficulty, and partly because it requires considerable cooperation of the patients most of whom suffer from various difficulties in

execution of the given movement tasks (Shibasaki et al., 2006). Processing of the data has been a limitation, but software is available for back-averaging (Vial et al., 2020).

The initial slope of BP, called ‘early BP’ or BP1, begins about 2 s before the movement onset in the pre-supplementary motor area (pre-SMA) with no site-specificity and in the SMA proper according to the somatotopic organization, and shortly thereafter in the lateral premotor cortex bilaterally with relatively clear somatotopy (Shibasaki et al., 2006) (Table 2). About 400 ms before the movement onset, the steeper negative slope, called ‘late BP’ or BP2 (also referred to as NS’), occurs in the contralateral M1-and lateral premotor cortex with precise somatotopy. These two phases of BP are differentially influenced by various factors, especially by complexity of the movement which enhances only the late BP. The BP can be used to investigate the pathophysiology of various movement disorders. BP-like activity similar to that seen before voluntary muscle contraction is also seen before volitional motor inhibition or muscle relaxation. Since BP with a typical waveform and temporospatial pattern does not occur before organic involuntary movements, BP can be used for detecting the participation of the ‘voluntary motor system’ in the generation of involuntary movements in patients with functional movement disorders (Kamble et al., 2016) (Fig. 19).

Frequency-based analysis of movement-related cortical activities

In addition to the analysis of field potentials described above, cortical activity can also be studied by analyzing the power change of EEG oscillations in the frequency domain. Power decrease in the alpha or beta band time-locked to an event or a task, which is called event-related desynchronization (ERD), is considered to represent increased activation of the corresponding cortical area while power increase, event-related synchronization (ERS), is associated with return to the resting condition or even decreased activation (Bai et al., 2005, Oishi et al., 2007, Savic et al., 2020). Advances in the digital EEG equipment and computer processing enabled applying these methods for analyzing even high gamma activity (100 to 300 Hz) to the ECoG dataset (Crone et al., 2006). Movement-related power decrease (desynchronization) and movement-related power increase (synchronization) in the alpha and beta frequency range are observed over the relatively wide region of the sensory and motor areas, whereas movement-related desynchronization or synchronization of the gamma frequency range is observed over a relatively limited area of S1-M1. All these analysis methods can be applied to an ECoG dataset for functional mapping of the motor cortex (Fig. 20) (Neshige et al., 2018).

Application of movement-related EEG/MEG to brain-machine interface (BMI)

If we can detect intention to move by recording cortical activities by EEG or MEG, it can be applied to rehabilitation of patients with motor paralysis. This brain-machine interface (BMI) or brain-computer interface (BCI), however, requires a single-trial analysis of the cortical activities without depending on averaging across trials. Since the BP is as small as 10 μV, it is extremely difficult to extract it from the background activities in a single-trial analysis. Therefore, oscillation-based approach detecting the power change of certain frequency bands is more commonly applied for this purpose (Fukuma et al., 2018, Abiri et al., 2019).

6. Coherence

Coherence can be estimated in the frequency domain which measures the linear association between two simultaneously recorded signals. It is the most widely used analytical tool to look at the relation or connection between two electrophysiologically recorded signals in movement disorders and is therefore dealt with in a separate section. Coherence analysis results in a coherence spectrum displaying the degree of correlation between 0 and 1 (ordinate) for each frequency bin (abscissa), with 0 indicating no correlation at all and 1 indicating perfect correlation. The level of significance is mathematically defined. It depends on the length of the recordings and the desired frequency resolution and is typically displayed as a horizontal line in the spectrum above which coherence values can be regarded statistically significant (Fig. 21 (Halliday, 1998, Muthuraman et al., 2008)). Coherence analysis algorithms are part of some available EEG and EMG systems and of most advanced signal analysis platforms (e.g., MATLAB, FieldTrip toolbox (Oostenveld et al., 2011)).

In movement disorders, coherence analysis is most commonly applied to non-invasively acquirable signals, that is EEG/MEG, surface EMG from one or several muscles and accelerometry from one or different limbs. Oscillations occurring in the same narrow frequency band with respective peaks in the frequency (power) spectrum (e.g., tremors) are not necessarily correlated and only coherence analysis can detect a possible correlation (Fig. 21). Looking at the coherence between a broad band signal without clear frequency peaks (e.g., EEG) and a signal clearly focused in one frequency band (e.g., tremor EMG) coherence analysis can detect relevant activity of the broad band signal in this specific frequency range (Fig. 22).

Significant coherence values indicate coupling between the two signals in the frequency range in which the coherence rises above the level of significance. The neurophysiological basis of this coupling can be diverse. Signals could be recorded from two nodes of the same network (e.g., cortico-cortical coherence), they could be driven by the same higher order center or process (e.g., musculo-muscular coherence) or one signal could be transmitted to or driven by the other (e.g., corticomuscular coherence). Whereas the site of recording in the motor system gives rise to assumptions concerning the type of interaction other more advanced mathematical methods (e.g., phase spectra, partial directed coherence, Granger causality) beyond pure coherence analysis are necessary to gain direct evidence.

As the frequency ranges of pathological activity are well known in a number of movement disorders (e.g., tremor frequency, beta band activity in PD) the finding of coupled activity in these specific frequencies, changes of this with test-treatments or in specific tasks and also a lack of coupling between certain recording sites can give clues as to the pathophysiology of the disease under study.

A common concern in coherence analysis is spurious results due to shared artefacts in both recordings mimicking a physiological or pathophysiological meaningful interaction between the two signals. Movement artefacts caused by cable or electrode movements are a common phenomenon. In EMG recordings these can be eliminated by a high pass filter (for EMG-preprocessing see first part of this chapter). There is an ongoing debate as to whether

rectification of surface EMG is detrimental (McClelland et al., 2012) or advantageous for the detection of coupling in certain frequency ranges (Ward et al., 2013). However, this may depend on the frequency band and task condition of interest (Dideriksen et al., 2018). To fully understand the effects of rectification more systematic comparative studies are needed, which should include simulations and real EMG data.

In case of EEG recordings, the movement frequencies are within the range of physiological and pathological EEG activities which makes a technical elimination difficult. Therefore, great care must be taken during recordings to avoid swinging cables or wobbling electrodes. In particular during parallel recordings of EEG and EMG in higher amplitude tremors this cannot always be avoided completely. Typical reference electrodes in EEG like mastoids or earlobes are especially prone to movement artefacts. Therefore local reference schemes (current source densities, Hjorth transformation) are recommended (Hjorth, 1982, Mima et al., 1999) and show the best results for EEG-EMG (corticomuscular) coherence. Movement artefacts in EEG-EMG coherence are typically widely distributed in most of the recorded electrodes on both sides of the skull. In particular they do not follow the physiological somatotopy (e.g., typical maximal coherence in the contralateral central hand area when relating EEG to a recorded forearm muscle). Thus, they can usually be detected if larger electrode arrays are used, at least 10/20montage and, if possible, even higher EEG electrode densities. If only a few central electrodes of interest are recorded, detection of such artefacts is hardly possible. In addition, simple coherence which is a parametric method does not give a robust estimation for signals with non-Gaussian distribution and noisy components. Another way would be to use non-parametric methods based on the median of auto-/cross-spectra for the estimation of coherence (Nasseroleslami et al., 2019). As MEG is reference free and typically recorded with a fixed high-density sensor array, artefacts are less common and can be detected as described for EEG.

In case of EEG-EEG (cortico-cortical) coherence, shared movement artefacts leading to spurious results are more difficult to spot. Due to volume conduction the same oscillatory activity in a region of the brain can be picked up by many EEG electrodes, and this can lead to strong coherence between electrodes not necessarily reflecting interactions between the underlying brain regions. Field spread in MEG can produce similar effects (Winter et al., 2007). Local reference schemes (e.g., Hjorth transformation) can reduce this effect in EEG recordings and the imaginary part of the coherence reduces instantaneous volume conduction effects (Nolte et al., 2004). However, it can be difficult to interpret as it is blind to synchronizations between brain areas without time lag. Partial coherence can also be used to control (‘partialize’) for the effect of volume conduction of dominant oscillatory activity as recorded from a third distant brain region; e.g., the effect of the common spread of alpha-rhythm to frontal electrodes can be controlled for by partializing for an occipital electrode (Mima et al., 2000). However, the origin of many other oscillatory brain activities is less clear and can change over time, so partial coherence is not helpful in controlling for their volume conduction effects.

The extent of volume conduction depends on the relative location of the electrodes with respect to the generators of oscillatory activity in the brain. This must be kept in mind when comparing EEG-electrode-to-electrode coherence between different subjects or different

sessions. For intraindividual comparisons between different conditions or tasks in the same session the extent of volume conduction has little influence. However, changes in the distribution of oscillatory activity in the brain cannot be separated from true changes in cortico-cortical interactions in EEG-EEG coherence analysis. One way to circumvent these problems is to apply an inverse method deducing the location and signal of oscillatory sources in the brain from the superficially recorded EEG signals. Components of the signal in the EEG electrodes originating from specific brain regions are extracted by a spatial filter. Coherence between the signals from different brain regions can then be calculated and even combined with corticomuscular coherence (Gross et al., 2001). There are no unequivocal inverse solutions, but performance improves with large electrode arrays and knowledge of exact electrode position with respect to individual MRI-anatomy. These methods have contributed to our knowledge on the central oscillating networks of different tremors (Fig. 23). Whereas coherence between the peripheral tremor oscillations and EEG activity in the electrodes above the contralateral sensorimotor cortex can be shown similarly for almost all pathological tremors, it is the central network and its interactions as resolved by coherent source analysis that offers clues to the differential pathophysiology of tremors (e.g., (Muthuraman et al., 2018)). Furthermore, the coherence can also be used as a measure to infer causality in both domains, namely in frequency and time. First, we estimate time-dependent multivariate (MVAR) coefficients; the next step is to use these auto-regressive coefficients to infer causality between the time series. By calculating the time dependent MVAR coefficients at each time point, we can also calculate time resolved partial directed coherence (PDC). In this way we can infer causality between any two signals (Muthuraman et al., 2018).

Coherence between different peripheral signals (e.g., accelerometry and EMG) from different limbs or within the same limb is more readily available and surface EMG and accelerometry/kinesiology recordings are common tools in the clinical neurophysiological work-up of movement disorders (see part 1 and 2 of this chapter). Coherence between surface EMG signals from agonistic and antagonistic muscles of the same limb are mostly interpreted as common central drive to the muscles in the respective frequency band. For example, in dystonia the intermuscular coherence between muscles of the same affected limb is known to be increased at low frequencies (Grosse et al., 2004) and a reduction of this could be useful for objective monitoring of therapeutic interventions (Doldersum et al., 2019). One concern in EMG-EMG coherence between neighboring muscles is that coherence could be artificial due to electrical crosstalk, again due to volume conduction, that is instantaneous propagation of the signal from more distant muscles not directly underlying the surface electrodes. A discontinuous sharp peak at zero time lag in the cross-correlation function can help to detect this (Raethjen et al., 2000), but as for EEG volume conduction effects, it is difficult to differentiate between instantaneous crosstalk and pathophysiological meaningful synchronization without time lag.

A pathophysiologic characteristic of most organic tremors manifesting in different parts of the body is a lack of significant coherence because of independent oscillations in each affected limb (Raethjen et al., 2000). One exception to this rule is primary orthostatic tremor. The high frequency oscillations (13-18 Hz) of primary orthostatic tremor are highly synchronized (coherent) throughout the body, and intermuscular coherence between

different limbs is one diagnostic clue (Koster et al., 1999). As a second exception, coherence of low frequency tremors (3-10 Hz) between different limbs is a sign of a functional tremor (Raethjen et al., 2004, Schwingenschuh et al., 2016). The fact that independent voluntary rhythmic movements in different limbs cannot be maintained by normal subjects and the assumption that functional tremors rely on the same mechanisms led to the development of the (coherence) entrainment test (McAuley et al., 2004). In functional tremor rhythmic voluntary tapping at a lower frequency in a non-affected or less affected limb often entrains the tremor to the tapping frequency, and this can be detected by a significant coherence between EMG or accelerometry at this frequency. Although this test is diagnostically very useful care must be taken that significant coherence with high amplitude strenuous tapping movements is not over-interpreted. When it is performed accelerometrically a mechanical resonant coupling between the limbs under study could lead to small but highly coherent artificial oscillations at the voluntary tapping in addition to the tremor oscillation. Probably owing to physiological (Carson, 2005) or pathologically enhanced (Cox et al., 2012) mirror innervation with effortful contralateral tapping small coherent activity may overlay the tremor-bursts even in EMG recordings of organic tremors (unpublished observation). Thus along with the coherence spectrum between the tapping limb and the tremor limb both power spectra should always be quantified. The change in tremor frequency towards or on the tapping frequency seems to be the most valid hint at a functional tremor in the entrainment test (Zeuner et al., 2003, Schwingenschuh et al., 2016).

A measure of linear dependency between two signals at each frequency coherence is not completely blind to many non-linear associations (Brillinger, 2001). However, its reliability decreases, and the nature of the coupling is not resolved. One common method to detect non-linear connections is mutual information but there are others (e.g., phase lag index, Granger causality, transfer entropy) and there is no broad consensus as to which yields the most reliable results for biological signals like EEG and EMG. Often the results are not frequency specific and there is no straight forward definition of the level of significance for these methods. Interactions between different frequency bands seem to be a common way of (non-linear) communication especially between different brain regions and methods to analyze this cross-frequency coupling can be more powerful to detect certain pathophysiological aspects of movement disorders and possible mechanisms of action of neurostimulation (Muthuraman et al., 2020). The cross-frequency coupling (CFC) can be divided into many types. When dealing with modelled interactions, bispectrum and bicoherence give robust estimates. With real electrophysiological data which are non-linear and noisy in nature, CFC is robust mainly phase to phase, phase to frequency, phase to amplitude, and power to power. The phase to amplitude is well-known and a widely used variant in both animals (Axmacher et al., 2010) and humans. Also we recently showed power-to power CFC in Parkinson’s disease deep brain stimulated patients (Muthuraman et al., 2020).

In conclusion, coherence is a well-established measure yielding statistically clear results. Care must be taken to avoid and detect spurious coherence introduced by movement artefacts, mechanical resonance or volume conduction. With this in mind coherence analysis substantially extends the neurophysiological perspective on oscillatory activity and

motor phenomena in movement disorders, and it can aid their diagnosis. Its place in the neurophysiological diagnostic work-up-routine has yet to be established.

7. Polysomnography

Polysomnography (PSG) is the main diagnostic tool used in sleep medicine and consists of a multi-parameter recording study of several different signals obtained by electrodes and transducers placed in strategic places of the body. The first goal of the test result is to score sleep stages characterizing sleep architecture that is then graphically represented with the so-called “hypnogram”. The second goal is to identify the presence and severity of a sleep disorder.

The full laboratory PSG is recorded during the whole night and requires continuous supervision and control by an accredited technician. In some instances, such as for shift workers and subjects with circadian rhythm sleep-wake disorders, it can be performed at other times of the day. The basic physiological signals included in a PSG recording are the electroencephalogram (EEG) – at least three channels from the frontal, central, and occipital areas of one hemisphere, referred to the contralateral mastoid (for example F3-M2, C3-M2, and O1-M2), electrooculogram (EOG) – at least two channels from 1 cm above and 1 cm more lateral than the lateral canthus of one eye and from 1 cm below and 1 cm more lateral than the lateral canthus of the other eye, both referred to the same mastoid, surface-recorded electromyogram from the chin and tibialis anterior muscles (EMG) and electrocardiogram (ECG) (Berry et al., 2020). For the study of sleep-related breathing disorders (sleep apnea), signals that explore the respiratory functions are included, such as oronasal airflow and respiratory effort measures, as well as peripheral pulse oximetry, capnography and snoring sound by a microphone.

Less complex tests than the full laboratory PSG can be performed, such as cardiorespiratory monitoring, which usually includes only the channels for respiration and ECG monitoring, and unsupervised “Out of Center Sleep Testing” (OCST). Wearable sensors can be used to monitor movements during the night, as has been done successfully in patients with Parkinson disease (Zampogna et al., 2020).

PSG must be performed by board-certified technicians in Sleep Medicine; however, this is not always possible and other technical staff, such as neurophysiology technologists, nurses, respiratory therapists, sometimes perform PSG. Board-certified technicians in Sleep Medicine are often involved in sleep staging of PSG recordings but the interpretation of PSG studies can only be done by medical personnel with specific training in Sleep Medicine. Sleep staging is carried out with the American Academy of Sleep Medicine criteria (Berry et al., 2020) which define the rules to identify, beside wakefulness (stage W), three NREM sleep stages (N1, N2, and N3), and REM sleep (stage R). These stages correspond, to a large extent but not completely (Danker-Hopfe et al., 2009, Novelli et al., 2010), to the sleep stages previously defined by Rechtschaffen and Kales in 1968 (Rechtschaffen et al., 1968) who indicated them as S1, S2, S3, and S4, in NREM sleep (the new N3 includes the previous S3 and S4).

Important information can be obtained from PSG, concerning both sleep structure (e.g., sleep latency, REM sleep latency, awakenings after sleep onset, total sleep duration, percentages and the duration of each sleep stage, etc.) and clinically relevant information allowing/supporting the diagnosis of different sleep disorders, in particular movement, behaviors, respiration, cardiovascular parameters, etc. In addition, based on the clinical features of each patient, PSG allows including the recording of additional signals useful for the detailed description of the individual sleep problem (for example, additional EMG channels such as the recording of masseter muscle contractions, body temperature, esophageal pH, etc.).

Video-PSG is an extension of PSG with the addition of synchronized video recording. The possibility to analyze the video of the movements or behaviors accompanying the signal features captured by PSG provides an extremely powerful tool for the assessment of sleep disorders such as parasomnia (NREM and especially REM sleep parasomnia, such as REM sleep behavior disorder or RBD) and sleep-related seizure disorders.

As introduced above, PSG is a very important exam within the diagnostic process of sleep-related movement disorders which include a variety of conditions. The International Classification of Sleep Disorders, 3rd ed. (American Academy of Sleep, 2014) includes in this category: Restless Legs Syndrome (RLS), Periodic Limb Movement Disorder (PLMD), Sleep Related Leg Cramps, Sleep Related Bruxism, Sleep Related Rhythmic Movement Disorder (RMD), Benign Sleep Myoclonus of Infancy, Propriospinal Myoclonus at Sleep Onset, Sleep Related Movement Disorder Due to a Medical Disorder, Sleep Related Movement Disorder Due to a Medication or Substance, Sleep Related Movement Disorder-Unspecified, Isolated Symptoms and Normal Variants (Excessive Fragmentary Myoclonus, Hypnagogic Foot Tremor and Alternating Leg Muscle Activation, Sleep Starts or Hypnic Jerks).

RLS is a common neurologic sleep-related movement disorder, affecting both children and adults, characterized by an irresistible compulsive urge to move the legs, often associated with dysesthesias. RLS exclusively occurs or is enhanced at periods of rest, the urge to move and the associated dysesthesias are heightened at night, and both are partially or totally relieved by movements (Allen, 2014). All these features are essentially subjectively reported by patients with RLS; however, the presence of a high number of periodic leg movements during sleep (PLMS) can be found in the PSG of up to 90% of adult patients with RLS (Aurora et al., 2012) and have been indicated to be a motor sign supporting the diagnosis, in particularly when it is dubious or in children (Allen, 2014). Also PLMD is characterized by the presence of excessive PLMS on PSG (PLMS/hour >5 for children, >15 for adults) that cause significant sleep disturbance impairment in normal daytime functioning; in PLMD, PLMS and related symptoms are not better explained by another disorder (such as sleep disordered breathing, as an example) (American Academy of Sleep, 2014).

PLMS are currently defined as four or more consecutive leg movements separated from each other by a minimum interval of 10 s and a maximum of 90 s (Ferri et al., 2016) or, following a second and less updated set of criteria, by a an interval of 5-90 s (Berry et al., 2020) (Fig. 24). In recent years, a substantial amount of evidence has been produced on the

neurophysiological features and possible clinical significance of PLMS (Ferri et al., 2017) that are fully taken into account by the first set of scoring criteria cited above but not by the second set.

Other leg motor activities during sleep, such as alternating leg muscle activation (ALMA) and hypnagogic foot tremor (HFT) (American Academy of Sleep, 2014), can be detected by PSG that are very similar movement patterns of the feet and legs, occurring most often at sleep onset and correlated with arousals. These phenomena are suspected to be related to PLMS and RLS; however, this remains to be determined. ALMA during sleep is a quickly alternating pattern of the anterior tibialis muscles occurring at a frequency of approximately 0.5 to 3 Hz, lasting between 0.1 and 0.5 seconds, organized in sequences of alternating activations lasting up to 20-30 s (Fig. 25). HFT has several similarities to ALMA with foot movements occurring at the transition from wakefulness to sleep or during light sleep, recorded by PSG as recurrent EMG potentials at 0.3-4 Hz in one or both feet in a run of at least 4 events. In both ALMA and HFT, the EMG bursts are longer than those of myoclonus (>250 ms) and last usually less than 1 s. It should be mentioned that the term “high frequency leg movements” has been used for a similar pattern that reflects, probably, the same phenomenon.

RBD is a REM sleep parasomnia (rather than a sleep related movement disorder) in which the physiological atonia during REM sleep is lost or greatly diminished with the occurrence of dream-enacting behavior, often associated with nightmares (American Academy of Sleep, 2014). The presence of sustained or intermittent elevations of the submentalis muscle EMG tone or excessive phasic submentalis muscle twitching (or of upper and lower limbs) is a required PSG feature for the diagnosis of RBD (American Academy of Sleep, 2014). This PSG feature is called “REM sleep without atonia” (RSWA) (Fig. 26) which can be detected by a general and non-quantitative visual analysis or, better, with more quantitative assessments based on both visual and automatic approaches (Pulighedu et al., 2019). All these methods have been reported to show sufficient sensitivity and specificity for their application in both clinical practice and research settings and also seem to provide comparable results.

Sleep bruxism is characterized by grinding or clenching of the teeth during sleep, usually associated with sleep arousals (American Academy of Sleep, 2014). PSG is indicated when sleep bruxism is suspected in association with sleep disorders (sleep apnea, RBD), nocturnal seizures or oro-facial-mandibular disorders. PSG typically shows an EMG artifact recorded on the surface EEG leads, especially when referred to ear or mastoid electrodes (as for PSG standards) (Berry et al., 2020). Chin EMG electrodes are usually sufficient for the scoring of sleep bruxism; however, masseter and/or temporal EMG allow a clearer detection and quantification. An episode of sleep bruxism may consist of “rhythmic masticatory muscle activity” (RMMA - at least 3 rhythmic phasic contractions at a frequency of 1 Hz, lasting between 0.25-2 s) (Fig. 27), tonic (sustained contraction for more than 2 s) or mixed phasic-tonic masticatory muscle activities, associated with tooth grinding sound during sleep. Each episode has to be separated by a period of at least 3 s of stable background EMG to be scored as a new sleep bruxism episode. Classically, for the diagnosis of sleep bruxism, at least 4 episodes per hour of sleep have been considered to be required; however, more

recently, sleep bruxism has been graded as of low (>1≤2 episodes/hour), moderate (>2≤4 episodes/hour) or high intensity (>4 episodes/hour) (Lobbezoo et al., 2017).

Propriospinal myoclonus at sleep onset is a relatively rare motor disorder characterized by massive and symmetric jerks occurring during the transition from wakefulness to sleep, involving first the axial muscles of the abdomen, thorax or neck, and spreading rostrally and caudally to the other myotomes by means of slow propriospinal polysynaptic pathways (American Academy of Sleep, 2014). The jerks typically occur during relaxed wakefulness or drowsiness and are inhibited by mental activation and sleep onset. Propriospinal myoclonus can cause insomnia because the patients is not able to sleep for a long time, with the jerks appearing repeatedly but not periodically. In general, and differently from RLS/PLMS, the jerks disappear during sleep. Placing additional surface EMG electrodes over the axial muscles of the abdomen, thorax and neck allows to appreciate the spreading of muscle activation, rostrally and caudally, starting from the initial site of contraction and thus confirming the clinical diagnosis (Stefani et al., 2019).

Patients with RMD present recurrent episodes of stereotyped rhythmic body movements occurring predominantly during drowsiness before sleep or light sleep, which may involve the head, neck, trunk, or limbs, in isolation or in combination (Gwyther et al., 2017). The movements cause clinical consequences with disturbed sleep, significant impairment in daytime functioning, or self-inflicted injuries (American Academy of Sleep, 2014). Rhythmic movement episodes may last for seconds to several minutes. Movements can involve the head (head banging or *jactatio capitis nocturna*, head rolling) but also the body (body rocking) or, more rarely, the legs (leg rolling or leg banging). Although the diagnosis can be made clinically, videoPSG allows to better define the type and site of movements and appears to be especially useful when the diagnosis is doubtful or RMD occurs in association with other sleep disorders. The use of additional EEG and EMG leads, in particular limbs leads, may help to distinguish RMD from other sleep-related repetitive movements such as PLMS, ALMA or motor seizures. At PSG the rhythmic movements are characterized by a frequency of 0.5-2.0 Hz, they consist of at least 4 single movements forming a rhythmic cluster, and the minimum amplitude of a single rhythmic movement is at least two times the background EMG activity (Fig. 28).

Excessive fragmentary myoclonus can be seen in PSG recordings as repetitive and sometimes almost continuous, very brief (<150 ms) EMG potentials in various muscles, occurring asynchronously and asymmetrically, in a sustained manner, without apparent clustering. The current standards state that fragmentary myoclonus can be considered as excessive when there are more than 5 potentials per minute, sustained for at least 20 minutes of NREM sleep (Berry et al., 2020).

Neck myoclonus (head jerks) indicates the movement associated with a short stripe-shaped movement-induced artifact visible vertically over the PSG signals, especially during REM sleep. However, because it does not seem to be accompanied by any EEG abnormalities and not preceded by any premotor potential, as well as for its duration usually longer than that of the classical myoclonus and its occurrence exclusively during sleep, a different name has

been proposed for this motor phenomenon (“sleep-related head jerks”) (Wolfensberger et al., 2019) and its clinical significance is still under debate.

Very recently, a new condition has been identified in children and adolescents which has been named "restless sleep disorder" (RSD). Clinically, RSD is characterized by concerns for frequent nocturnal repositionings, body movements involving large muscle groups and non-restorative sleep. Video-PSG indicates that large body movements are frequent in children with RSD (>5/hour) and are distributed along the whole night (DelRosso et al., 2019).

In conclusion, video-PSG is a useful tool to diagnose and quantify the severity of various sleep disorders, in particular sleep-related movement disorders. It has the advantage to be flexible to adapt to new scoring rules, incorporate new technology (automated scoring) and to video monitor the patient. New abbreviated home systems are developed but polysomnography remains the gold standard for the diagnosis of many sleep-related movement disorders.

8. Neuroimaging

Neuroimaging is widely used to study motor control in the brain of healthy subjects and patients with movement disorders. Techniques include MRI, molecular imaging, electroencephalography (EEG) and magnetoencephalography (MEG) (Toga, 2015).

The most used technique to study brain function is functional MRI (fMRI) using Blood Oxygen Level Dependent (BOLD) contrast (Ogawa et al., 1990). BOLD contrast is based on neurovascular coupling and differences in magnetic susceptibility between oxygenated hemoglobin (oxyhemoglobin) and deoxygenated hemoglobin (deoxyhemoglobin). Oxyhemoglobin is diamagnetic and has no effect on the T2* signal. Deoxyhemoglobin is paramagnetic and disrupts the homogeneity of the magnetic field inducing a decrease in the T2* signal. During brain activation, local increases in oxygen consumption and deoxyhemoglobin concentration appear early and are quickly followed by a large and prolonged supply of oxyhemoglobin. The oxyhemoglobin / deoxyhemoglobin ratio increases (deoxyhemoglobin becomes diluted). This increase results in an increase in BOLD signal, which begins one to two seconds after the onset of neuronal activity and peaks after 8 to 10 seconds (Fig. 29A). Another technique to measure neurovascular coupling is functional near-infrared spectroscopy (fNIRS). fNIRS is a technique that allows real-time non-invasive monitoring of brain O2 saturation associated with brain activation, thanks to the absorption of near infrared light by oxy- and deoxy-hemoglobin. More recently, functional ultrasound imaging techniques have been developed in animals that may be used in humans during surgical procedures in the future (Dizeux et al., 2019).

The relationship between BOLD signal and neuronal electrical activity has been studied in animals by simultaneous recordings. Extracellular electrical signals include local field potentials and multi-unit activities (Logothetis et al., 2004). The low frequency (<500Hz) local field potentials (LFP) correspond to synchronous dendritic currents. High frequency (> 1kHz) multi-unit activity (MUA) potentials correspond mainly to the action potentials of

neurons. In general, a better prediction of the BOLD signal is obtained by LFPs (Logothetis et al., 2004). The BOLD signal can therefore be considered a reflection of the input and output electrical activity and the intracortical processing of an activated region (Hall et al., 2016)]. The BOLD signal does not generally make it possible to differentiate the inhibitory and excitatory activity of neurons. Although the hemodynamic response to brain activity is focal, observed near activated neurons, this response may spread over short distances to neighboring larger vessels, responsible for a certain loss of specificity.

Images sensitive to BOLD contrast are gradient weighted (T2*) echo planar (EPI) images. In a fMRI experiment, EPI images covering the entire brain are acquired in 1 to 3 seconds and repeated for several minutes while the subject under study performs the requested tasks (task-based fMRI) or is at rest (resting state fMRI). Task-based fMRI highlights differences in activity between different cognitive states or mental processes. It does not allow absolute quantification of the level of brain activity. In an fMRI study, subjects perform a series of tasks defined by the examiner in the experimental paradigm. There are two types of paradigms, block-design and event-related. Block-design paradigms alternate a succession of activation and reference phases. During these phases, subjects quickly repeat an identical predefined activity (motor, visual or cognitive activity). During activation, the hemodynamic response gradually increases until reaching a plateau 8-10 sec after onset of activation (Fig. 29A). Block paradigms provide a measure of the average activity during each block but do not allow to isolate variations in performance within a block. They are commonly used in clinical practice due to their simplicity. Event-related paradigms are most often used in cognitive science studies. An event-related paradigm seeks to isolate brain activity (i.e., BOLD signal variations) associated with each cognitive event, each type of stimuli or response (e.g., correct responses to wrong responses during a task). Responses and behavioral parameters of the subject when performing the tasks including motor or verbal responses, eye movements, skin conductance, or even the electromyogram or electroencephalogram, are recorded to ensure proper completion of the task and to evaluate subject’s performance. Because signal changes recorded for each individual stimulus are very small (the signal does not have time to reach the plateau of activation), it is necessary to average signal variations of a large number of stimuli (usually several tens).

Analysis of fMRI data aims at detecting voxels whose signal varies with changes in brain activation states within noise and artifacts. It takes into account the fact that BOLD signal variations are small (typically of the order of one percent) and that the number of voxels in a brain volume is very high (often of the order of a million voxels) to limit the risk of false negatives and false positives. The general linear model is most commonly used to detect voxels in which BOLD signal varies depending on the experimental model. Software provided by MRI manufacturers is able to provide activation maps while subjects perform tasks inside the scanner (real-time fMRI). Real-time fMRI is primarily used in clinical practice to monitor task performance in real time.

Another type of analysis using fMRI data is functional connectivity (Fig. 29B). Functional connectivity aims at quantifying the flow of information between two distant regions. Measures of functional connectivity between two distant regions of the brain are defined as the Pearson linear correlation coefficients between the average BOLD signals recorded in

these two regions (Fig. 29B). It is therefore a measure of statistical dependence, which can be calculated without a priori knowledge about the experimental conditions. Under certain circumstances, the causal influence of a region on another region can also be quantified using effective connectivity (Friston et al., 2010). Effective connectivity approaches aim to describe and quantify the causal influence of a region on an adjacent region during a task (Fig. 29B). Effective connectivity requires the definition of an a priori structural model describing the regions and the links between these regions. Two main techniques of effective connectivity are used, Structural Equation Modeling (SEM) and Dynamic Causal Modeling (DCM). Functional connectivity can be studied during task performance or in the rest condition (resting state fMRI). Resting state fMRI is based on the measurement of spontaneous low-frequency fluctuations in the BOLD signal (<0.1Hz) in the absence of an activating task or stimulus. Distant but functionally connected brain regions exhibit spontaneous fluctuations in BOLD signal that correlate (Fig. 30). Spontaneous fluctuations in the fMRI signal include fluctuations related to BOLD signal, due to neuronal activity in the brain at rest, but also to electronic noise from the MRI machine and to the subject's non-BOLD physiological noise (heartbeat, movements respiratory). Data analysis consists in extracting BOLD signal fluctuations at rest from noise and studying long-distance correlations. Resting state fMRI therefore allows the analysis of the functional communications of the brain. It does not require the active cooperation of the patient.

Limitations of BOLD fMRI include among others the sensitivity to head movements, the fact that the technique is not truly quantitative, the dependence on task performance, the low temporal resolution (of the order of a second), a modest sensitivity which often requires the inclusion of many subjects and explains the lack of reproducibility of results between studies which included a small number of subjects and used low statistical thresholds (Poldrack et al., 2017).

A number of other MRI techniques provide biomarkers that can be used to study the relationships between the motor system and the brain (Fig. 31). Another functional technique is arterial spin-labeling (ASL) perfusion imaging that quantifies the perfusion of brain tissue using magnetically-labeled arterial blood protons (Fig. 31A). Structural imaging provides markers of neurodegeneration allowing for instance to quantify brain atrophy (Fig. 31B) or degeneration of catecholaminergic neurons using neuromelanin-sensitive signal changes (Fig. 31C). Markers of tissue microstructure include T1 and T2 mapping (Fig. 31D), iron sensitive imaging (Fig. 31E), and diffusion imaging measurements, sensitive to microstructural changes in tissues that alter the regional diffusion properties of water molecules (Fig. 31F). Diffusion-based tractography provides indirect visualization and quantification of brain fiber tracts (Fig. 31G). These markers have been used to identify brain networks involved in movement disorders, and also to categorize patients with movement disorders from healthy subjects or other types of movement disorders, and to follow the course of the disease. Magnetic resonance spectroscopy (MRS) gives information about the absolute or relative concentrations of different metabolites in the brain. Concentrations of metabolites are sensitive to disease processes that affect the brain. Certain neurotransmitters such as glutamate, glutamine, and gamma aminobutyric acid can also be measured. MRS can thus provide qualitative and quantitative information about brain

neurotransmission. MRS can also provide information about changes in neurotransmitter concentration induced by transcranial magnetic stimulation of the cortex.

Molecular imaging is performed using Nuclear Medicine techniques (Strafella et al., 2017). It is based on the administration of radiolabeled tracers targeting a specific biological pathway and revealing, by a quantitative approach of the image, its bio-distribution. Brain function was formerly studied using oxygen-15 that indirectly measures blood flow, but this technique has been largely replaced by fMRI. Clinical imaging of movement disorders is usually conducted using SPECT (Single-Photon Emission Computed Tomography) and PET (Positron Emission Tomography). SPECT studies are conducted by the administration of 123I-FP-CIT or 123I-Ioflupane (DaTSCAN ©), a tracer of the presynaptic dopamine transporter (Fig. 32A). PET studies presynaptic dopaminergic function by evaluating dopa-decarboxylase activity using 18F –DOPA (Fig. 32B) or glucose metabolism using 18F-fluorodesoxuglucose (18F-FDG) (Fig. 32C). There are a number of other tracers that can quantify for instance other neurotransmitters such as noradrenalin and serotonin, neuroreceptors such dopamine, acetylcholine and serotonin receptors, peptides such as amyloid and tau, and microglial activation. PET imaging has several competitive advantages compared to SPECT, with in particular a three-dimensional detection at the acquisition, a better resolution, a better sensitivity, and a more precise quantification.

EEG and MEG techniques, described in detail in another section of this review, are non-invasive techniques that allow visualizing brain activity on a millisecond time scale in normal or pathological conditions. They offer a unique insight into the temporal dynamics of the processing of brain function. Since MRI, PET, and SPECT have good spatial resolution, but not temporal resolution, it is often useful to combine them with EEG or MEG. EEG and fMRI can be done simultaneously as used to advantage in epilepsy (Iannotti et al., 2020).

In healthy subjects, fMRI allows detailed study of the functional organization of the motor system at the level of the cortex, the basal ganglia but also of smaller of brainstem structures such as the substantia nigra and the pedunculopontine nucleus. Functional imaging studies provide a precise analysis of how different cortical regions interacted to generate simple or complex voluntary movements, internally or externally-guided movements, goal-directed movements or habitual control, to perform motor sequences, select or plan actions, learn new movements or perform them automatically (Doyon et al., 2009).

To show how these techniques can be helpful, some findings in several movement disorders will be illustrated as examples. In Parkinson’s disease, resting-state fMRI shows decreased coupling in the cortico-striatal sensorimotor network and between the striatum and the brain stem and increased coupling, interpreted as compensatory, in the associative networks as well as a remapping of cerebral connectivity within the primary motor cortex (M1) and the cerebellum (Lehericy et al., 2017). Connectivity changes are modulated by levodopa. The severity of motor symptoms correlates with dopaminergic dysfunction in the striatum using PET and SPECT, the reduction in neuromelanin content using neuromelanin-sensitive MRI, a surrogate marker of dopaminergic cell neurodegeneration, and the increase in iron content in the SN. In patients with rapid eye movement sleep behavior disorders (RBD), either idiopathic or in PD, neuromelanin-sensitive MRI confirm the relationships between

the severity of RBD, as shown by the increase in muscle tone during REM sleep, and the coeruleus/subcoeruleus complex (Garcia-Lorenzo et al., 2013).

In essential and orthostatic tremor, structural imaging, diffusion tractography and resting-state fMRI show abnormal structure and function in the cerebello-frontal network (Gallea et al., 2015). Structural and functional changes in the supplementary motor area, but not in the cerebellum, correlate with clinical severity.

In dystonia, the diversity of clinical phenotypes of dystonia has been associated with alterations of brain structure, function and connectivity using voxel-based morphometry, fMRI, and tractography. Traditionally linked to a dysfunction of the basal ganglia, recent evidence suggests that abnormalities extend beyond these circuits, including sensorimotor and cingulate cortices, the brainstem, and the cerebellum (Shakkottai et al., 2017).

In Tourette syndrome, studies show that there is a relationship between the appearance of tics and anatomo-functional abnormalities in the circuits that unite the cortex and the basal ganglia (Worbe et al., 2015). Abnormal control of the descending motor cortical pathways due to abnormal brain development could be the cause of the genesis of tics. The occurrence of tics is associated with several brain abnormalities including a modification of the activity of the cortico-striatal network (reduced functional activation of the primary motor cortex), neurochemical abnormalities (increased concentrations of gamma-aminobutyric acid in the additional motor zone), and rearrangements of white matter pathways.

In conclusion, neuroimaging techniques can be powerful physiological tools for studying the brain and complement more traditional clinical neurophysiological methods.

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Highlights

1. This review focuses on the most useful methods and techniques for the study of movement and movement disorders.
2. Tools that can be used to study movement include kinematics, kinetics, and the underlying muscle activity with EMG.
3. The brain activity driving movement can be studied with EEG, MEG, and functional MRI.

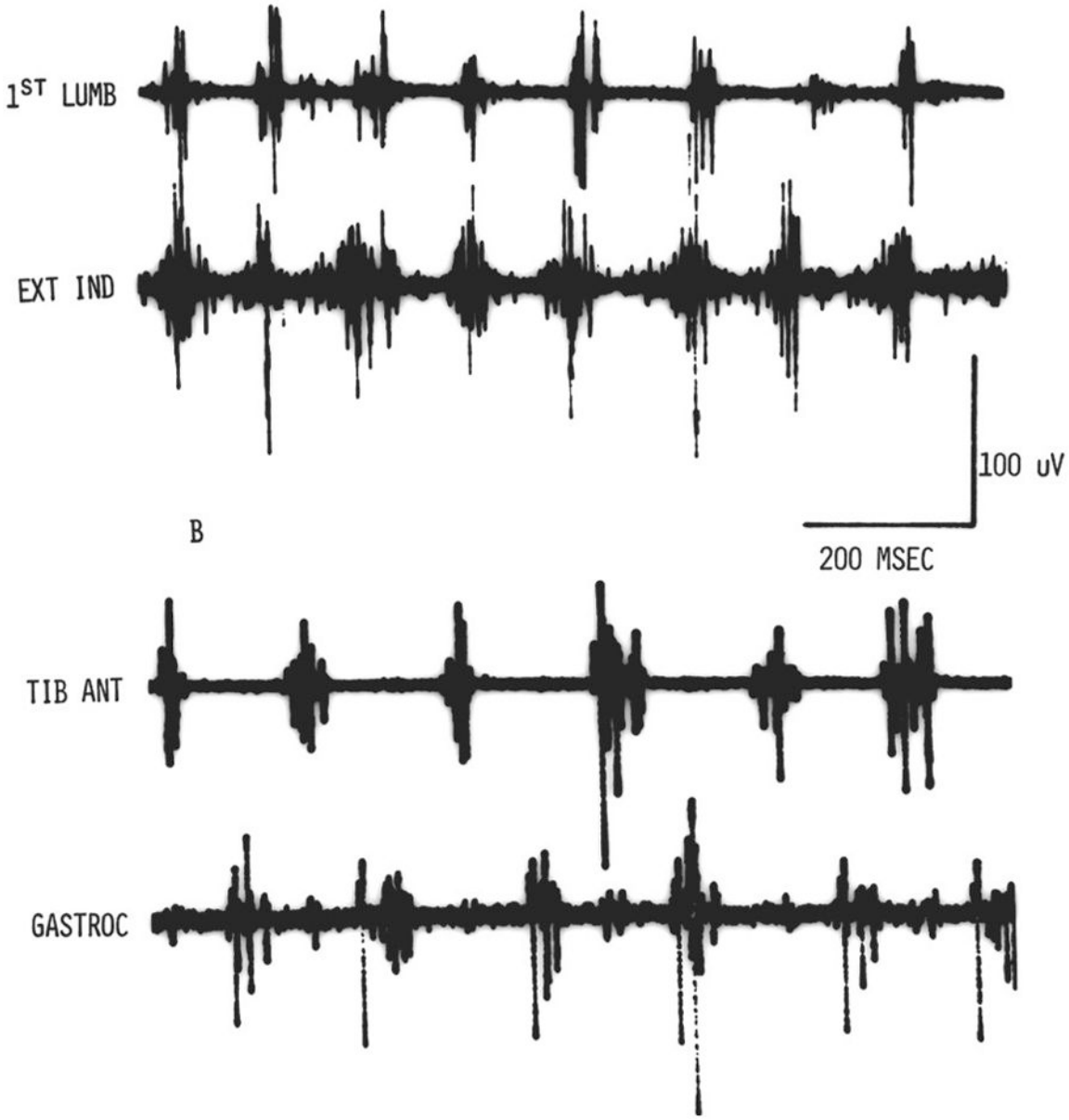

Figure 1.

Recordings from pairs of antagonist muscles in different tremors. (A) Needle EMG (electromyography) recordings from the first lumbrical (1st lumb) and the extensor indicis (ext ind) in a patient with essential tremor showing synchronous activation. (B) Surface EMG recordings in a patient with Parkinson disease showing alternating activity in tibialis anterior (tib ant) and gastrocnemius (gastroc). From (Sabra et al., 1984), with permission.

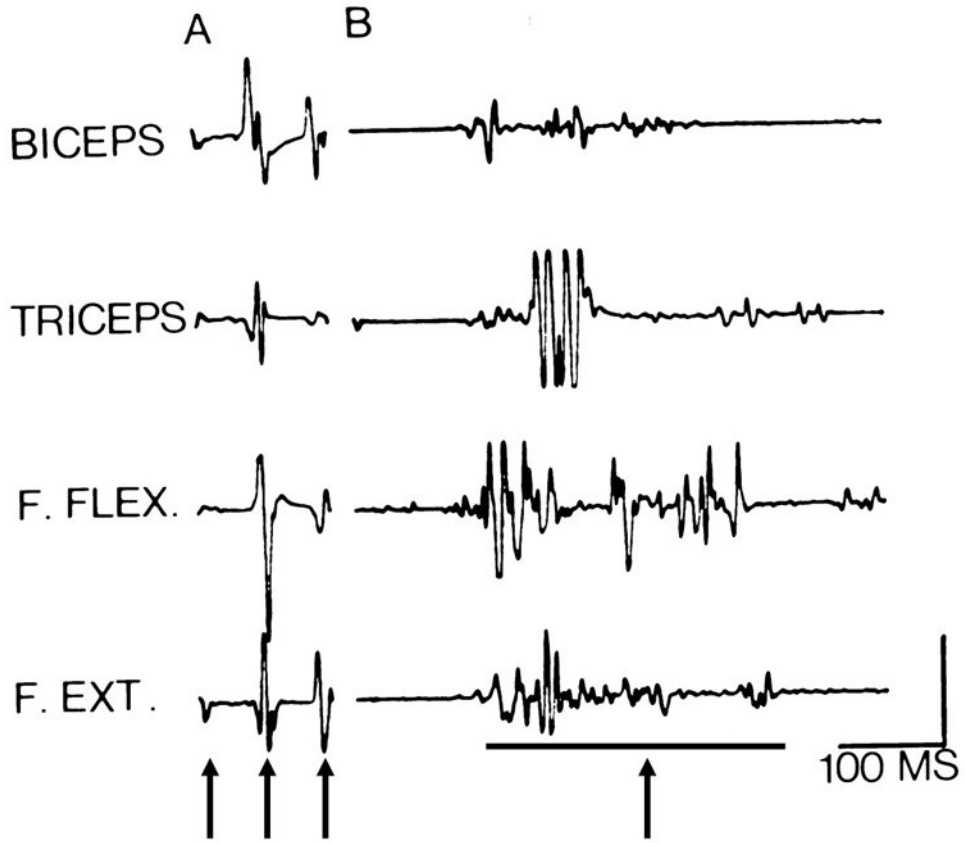

Figure 2.

Comparison of **(A)** 10-50ms, synchronous and **(B)** 50-100ms, alternating EMG (electromyogram) appearance underlying different types of myoclonus. A is from a patient with reticular reflex myoclonus, and B is from a patient with ballistic movement overflow myoclonus. Arrows in A point to 3 different myoclonic jerks. Arrow in B points to one myoclonic jerk. Vertical calibration is 1 mV for part A and 0.5 mV for part B. F.FLEX.=finger flexor muscles; F.EXT.=finger extensor muscles. From (Chadwick et al., 1977), with permission.

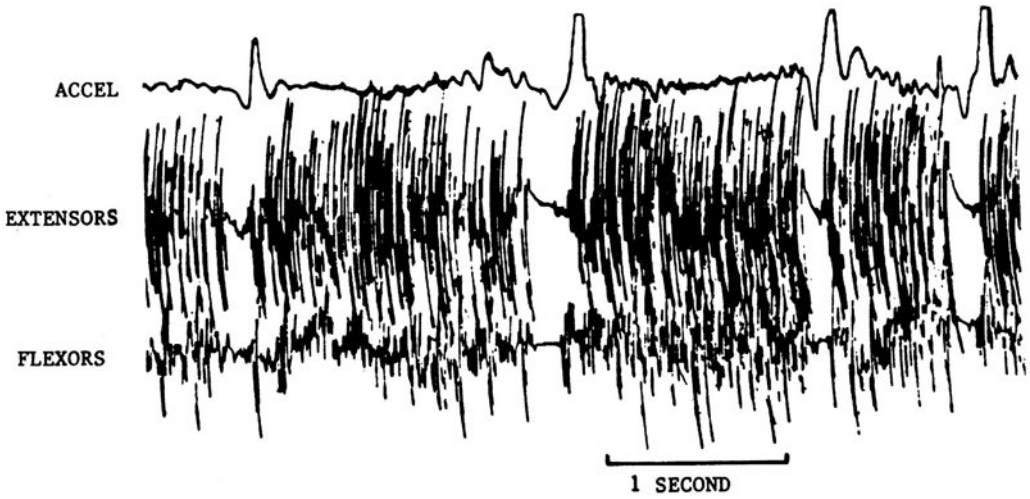

Figure 3.

EMG (electromyogram) and accelerometric (accel) recording of asterixis. Patient is holding arms up in front of him with wrists dorsiflexed. EMG is from flexors and extensors of the wrist and accelerometer was on the dorsum of the hand. From (Hallett, 1999), with permission.

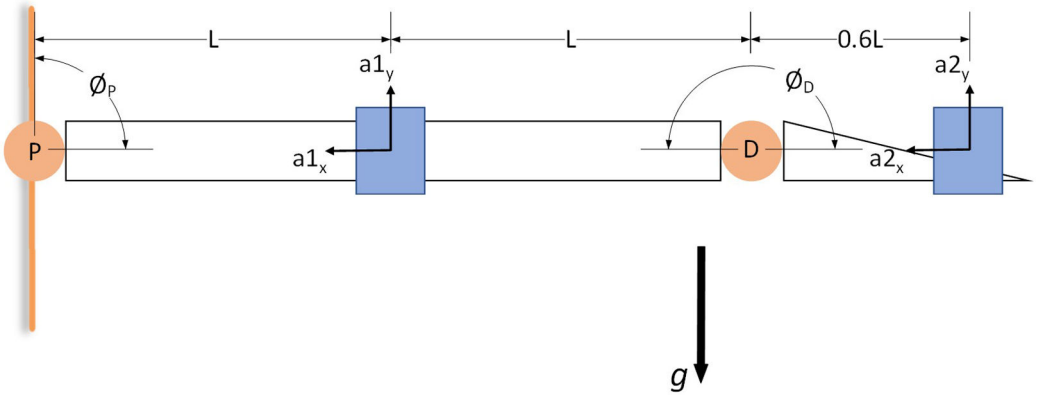

Figure 4.

A schematic diagram of two limb segments rotating about two joints P and D (orange circles) in the plane of the diagram. The axis of joint P is anchored in the plane of the diagram. Angular acceleration αP and αD at the two joints is the second derivative of joint rotation ØP and ØD. A transducer (blue box) is mounted on limb segments 1 and 2. The instantaneous vertical linear inertial acceleration of transducer 1 is a1y = L·αP, and if rotation at joint D is not allowed, the instantaneous vertical linear acceleration of transducer 2 is a2y = 2.6·L·αP. Also note that αP = (a2y − a1y)/1.6L. If joint P is fixed and rotation occurs only at joint D, the same angular acceleration at joint D will produce an instantaneous vertical linear acceleration of transducer 2 equal to 0.6·L·αD. The instantaneous vertical acceleration recorded by each accelerometer will be the inertial acceleration minus earth's gravity g (Elble, 2005). The arc length S for transducers 1 and 2 and rotation Ø (joint D is fixed) is L·ØP and 2.6·L·ØP, respectively. If joint P is fixed and the same rotation Ø occurs at joint D, the arc length of transducer 2 is 0.6·L·Ø. Thus, the perceived displacement and linear acceleration of an accelerometer are proportional to the distance of the transducer from the axis of rotation.

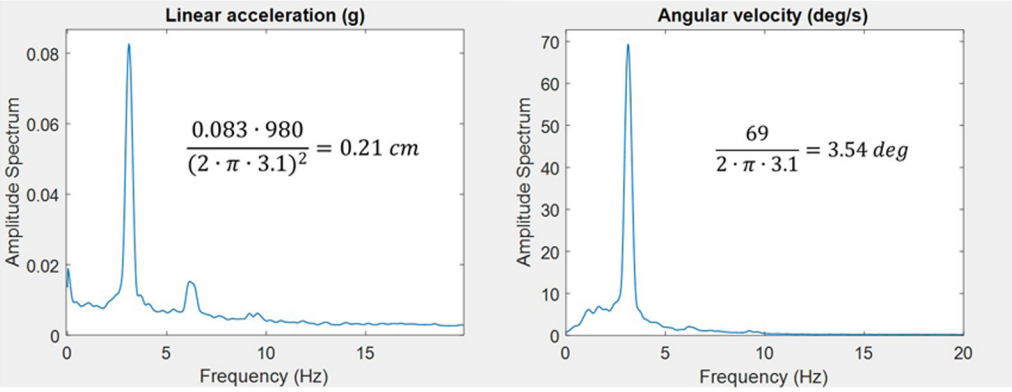

Figure 5.

Head tremor was recorded for 60 s with an inertial measurement unit (IMU) mounted at the vertex of the head of a 33-year-old woman with a very rhythmic 3.1-Hz horizontal head tremor, rated 2 on a 0-4 clinical rating scale (Elble et al., 2012). Note that the half peak-to-peak horizontal acceleration was only 0.083 g or 81.3 cm/s2. The half peak-to-peak displacement was estimated by dividing the acceleration by the squared frequency in radians/s. Thus, the accelerometer detected a half peak-to-peak displacement of only 0.21 cm. By contrast, the gyroscope recorded a 69 deg/s rotation in the horizontal plane, which corresponds to a half peak-to-peak rotation of 3.54 deg. Assuming a radial distance of 15 cm from the axis of rotation to the tip of the nose, this rotation would produce an arc length of movement = 15·2·**π**·3.54/360 = 0.93 cm or an average 1.86 cm peak-to-peak horizontal oscillation of the nose.

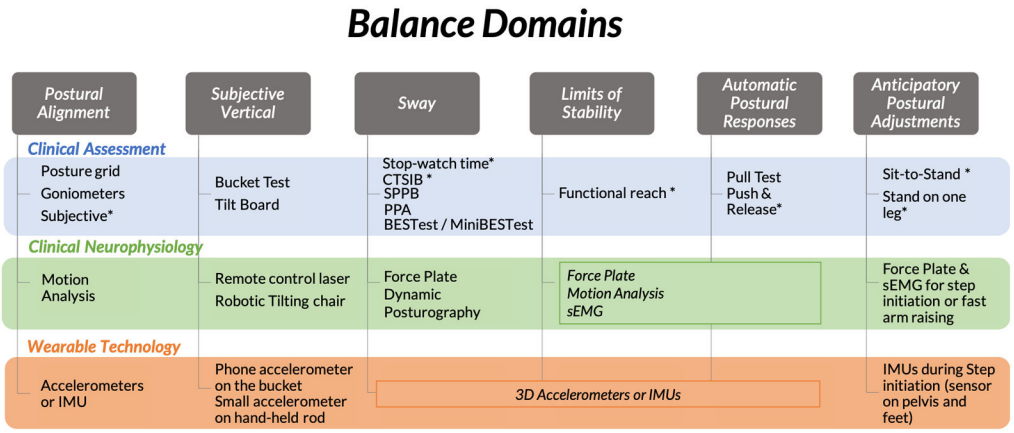

Figure 6.

Balance domains and 3 techniques (Clinical, Neurophysiology and Wearable Technology) to assess each domain. Abbreviations, CTSIB: Clinical Test of Sensory Interactions on Balance, SPPB: Short Physical Performance Battery, PPA: Physiological Profile Assessment, BESTest/MiniBESTest: Balance Evaluation Systems Test or Mini Balance Evaluation Systems Test. sEMG: surface electromyography; IMU: Inertial Measurement Units. Items with * are part of the BESTest

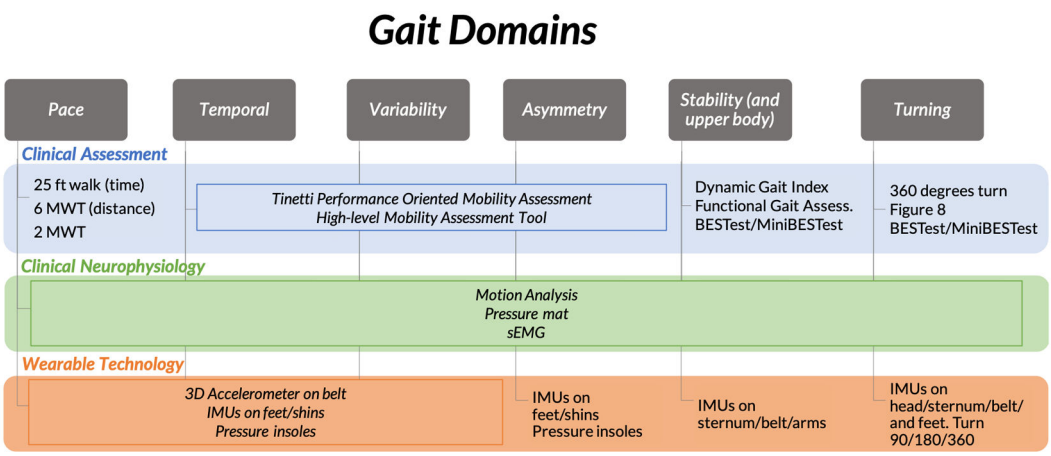

Figure 7.

Gait Domains and 3 techniques to assess each domain. Abbreviations, 25ft walk: time to walk 25 feet; 6MWT: 6-minute walking test; 2MWT: 2-minute walking test; BESTest/MiniBESTest: Balance Evaluation Systems Test or Mini Balance Evaluation Systems Test; Figure 8: time to walk a figure 8 shape; sEMG: surface electromyography; IMU: Inertial Measurement Units.

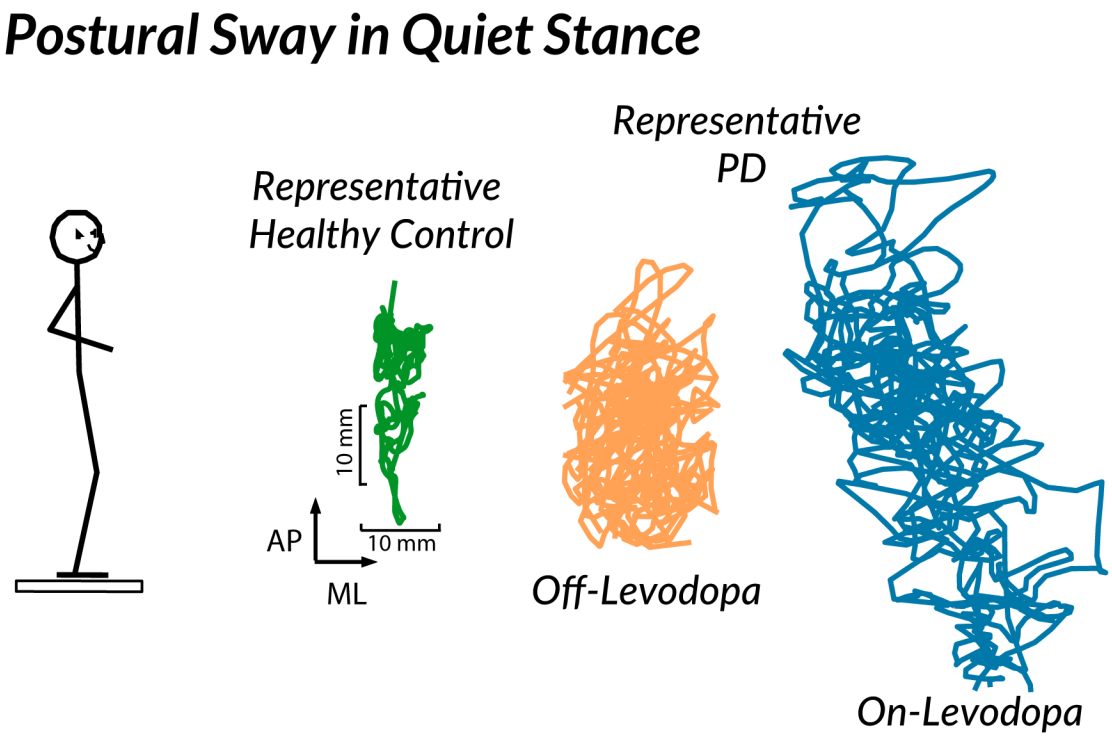

Figure 8.

Representative CoP (Center of Pressure) displacements in the horizonal plane (antero-posterior, AP and medio-lateral, ML) in a representative healthy control, and individual with Parkinson's Disease (PD), Off and On dopaminergic treatment from static posturography on a force plate (stabilogram).

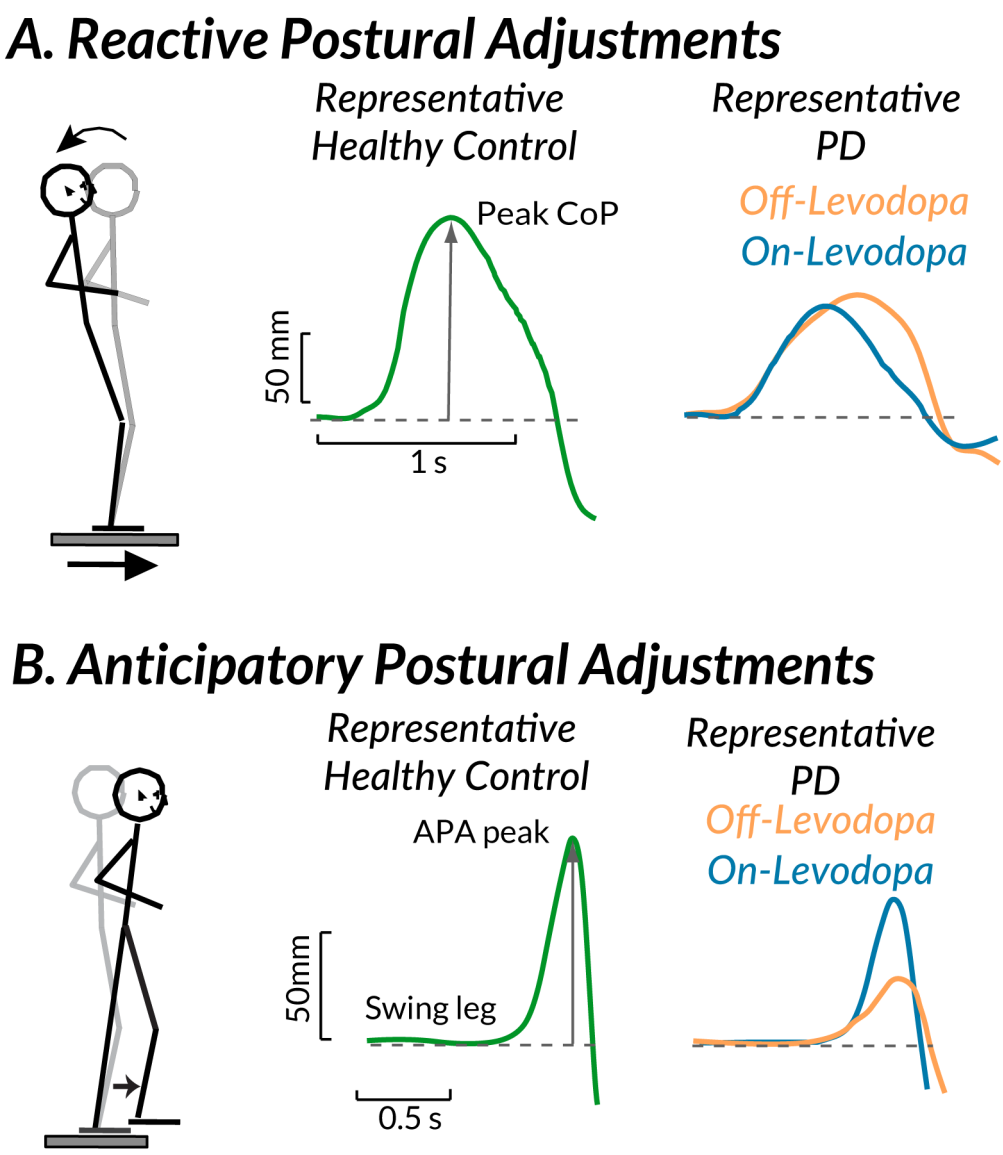

Figure 9.

Representative CoP (Center of Pressure) traces in a representative healthy control, and individual with Parkinson's disease (PD), Off and On dopaminergic treatment. A) Reactive Postural Adjustments to a forward platform transition that does not require a step, and B) Anticipatory postural adjustments prior to a voluntary step. Both automatic postural responses (APRs) and anticipatory postural adjustments (APAs) are slow and weak in people with Parkinson's disease. APRs do not improve with levodopa but APAs are larger On, than, Off levodopa.

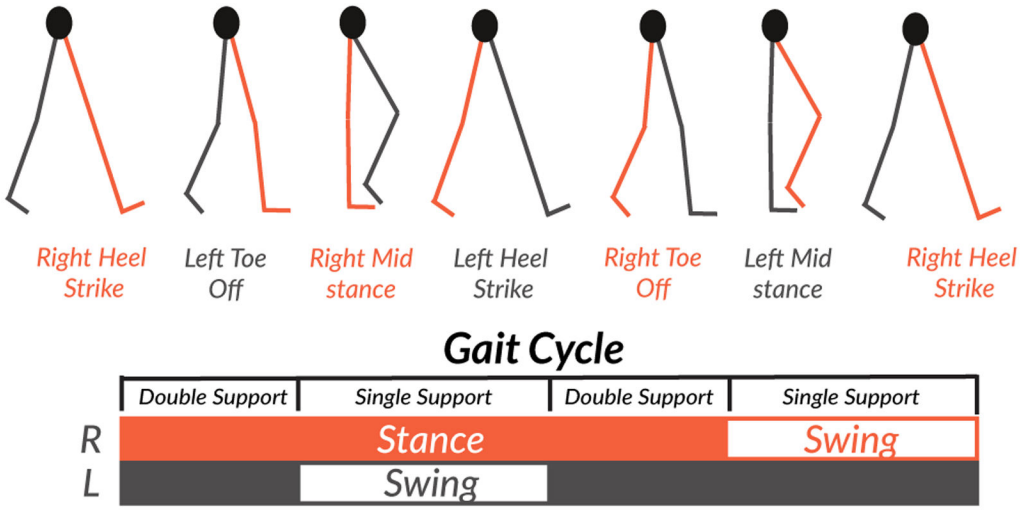

Figure 10.

Representative gait cycle for the right limb (red) starting from heel-strike (or initial foot contact) to the following right heel-strike.

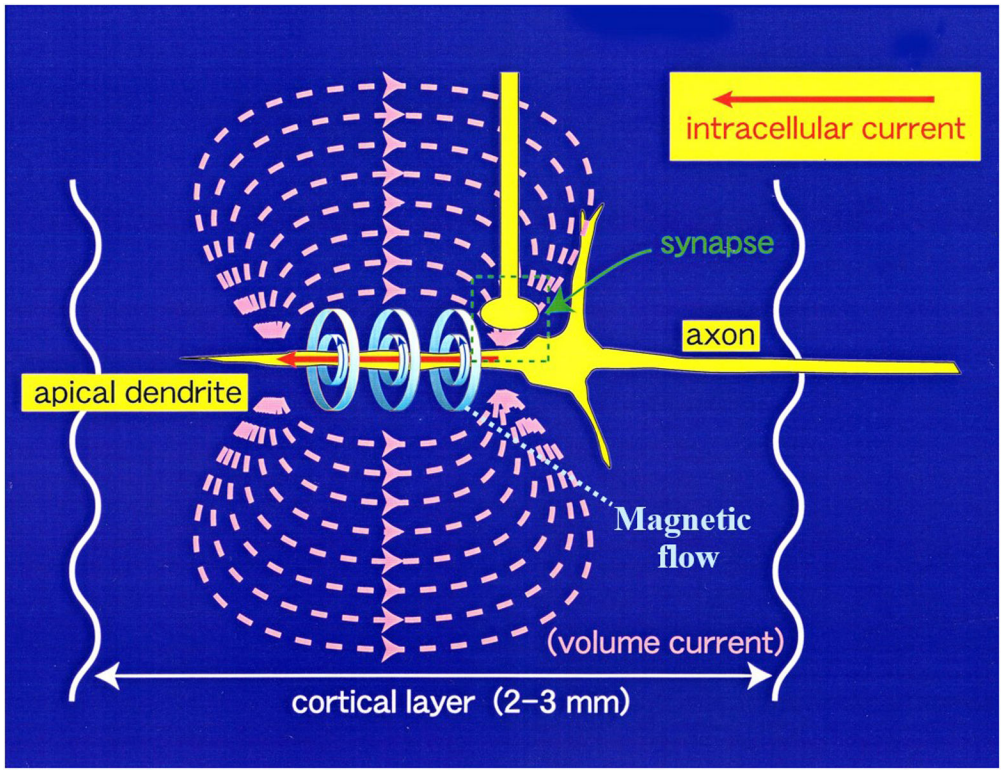

Figure 11.

Schematic diagram of electrical current and magnetic flow in the apical dendrite of large cortical neuron, showing the deep layer of the apical dendrite being activated. The intracellular current flows from the activated site to the superficial site while the extracellular current flows into the activated site. Magnetic flow occurs surrounding the intracellular current. (Designed by Prof. Takashi Nagamine of Sapporo Medical University)

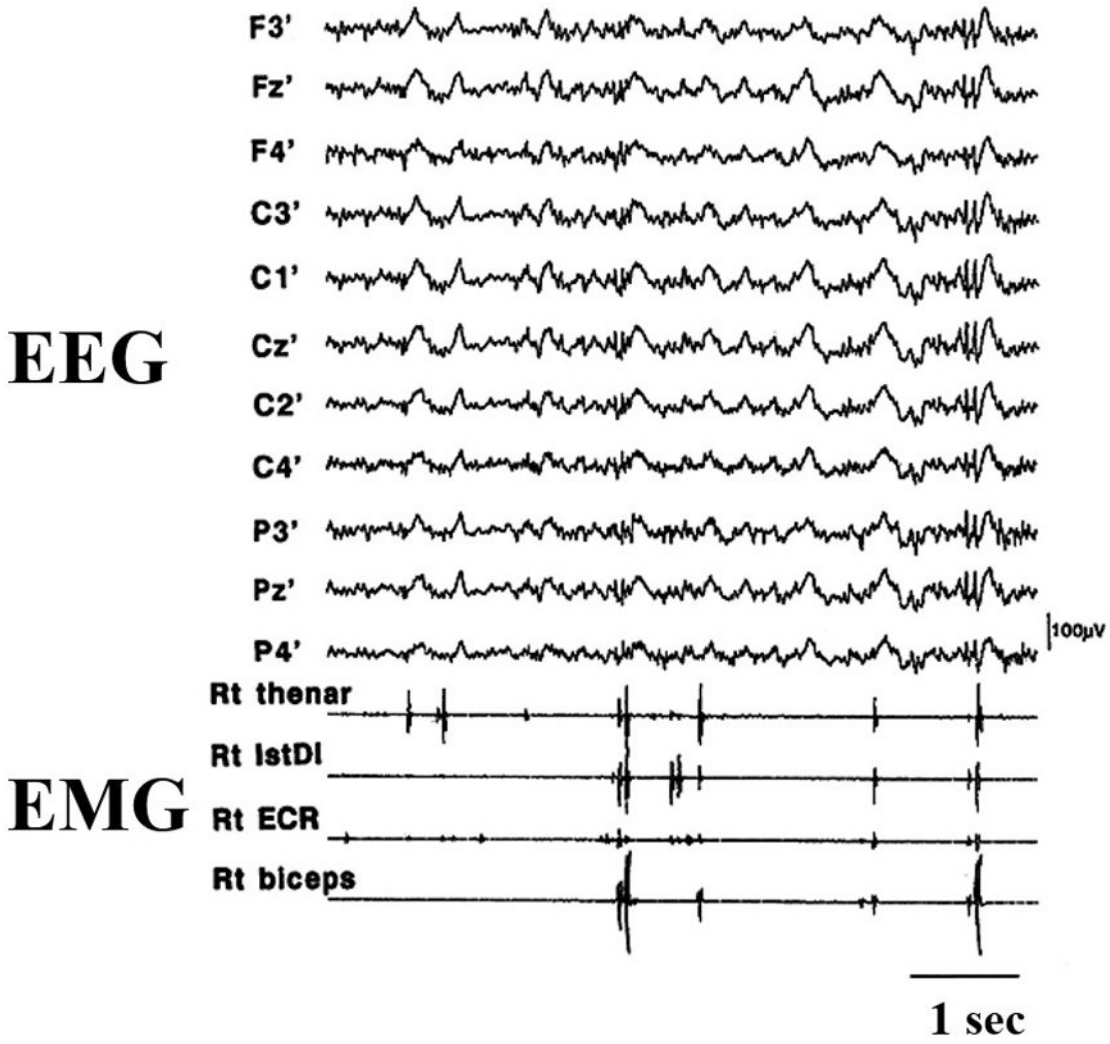

Figure 12.

EEG-EMG (electroencephalogram-electromyogram) polygraph in a patient with progressive myoclonus epilepsy. Frequent sharp discharges are seen in the EMG corresponding to myoclonic jerks, some of which are associated with EEG spikes. Rt thenar=right side thenar muscles, Rt 1stDI=right-side first dorsal interosseous muscle, Rt ECR= right side extensor carpi radialis muscle, Rt biceps= right side biceps muscle.

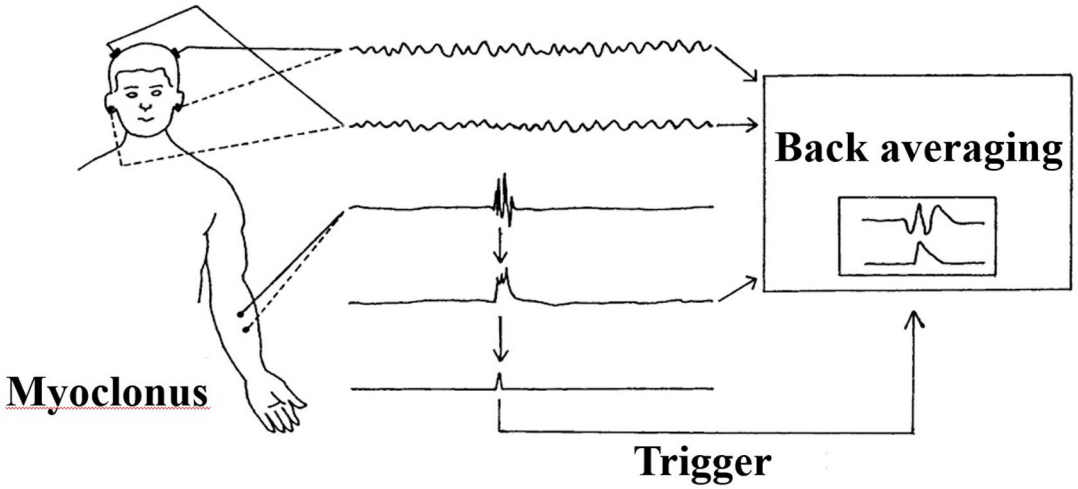

Figure 13.
Principle and method of jerk-locked back averaging.

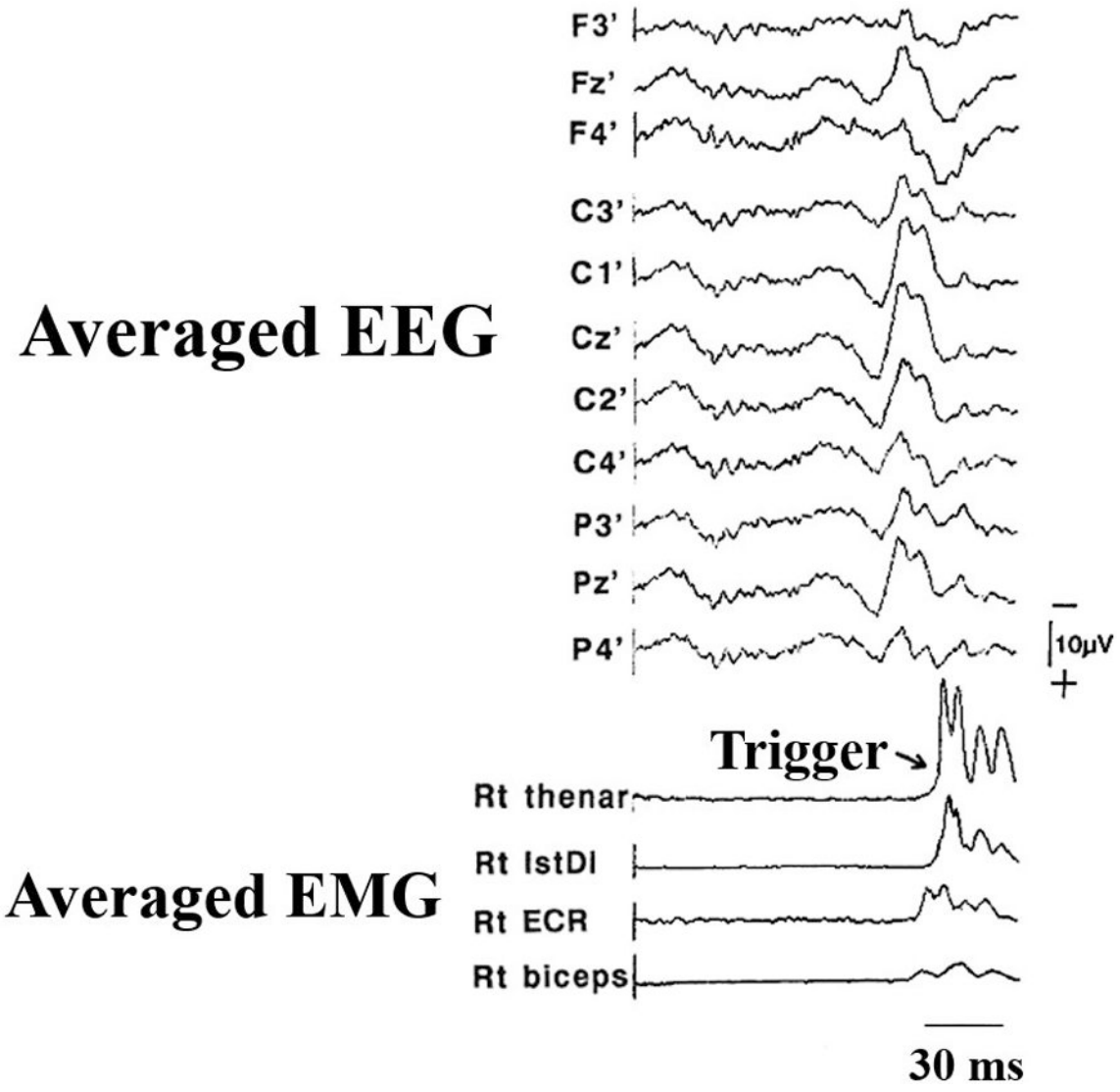

Figure 14.

Back averaged EEGs (electroencephalograms) time-locked to myoclonus of the right hand in a patient with progressive myoclonus epilepsy. See Figure 12 for the original polygraphic record of the same patient. Rt thenar=right side thenar muscles, Rt 1stDI=right-side first dorsal interosseous muscle, Rt ECR= right side extensor carpi radialis muscle, Rt biceps= right side biceps muscle.

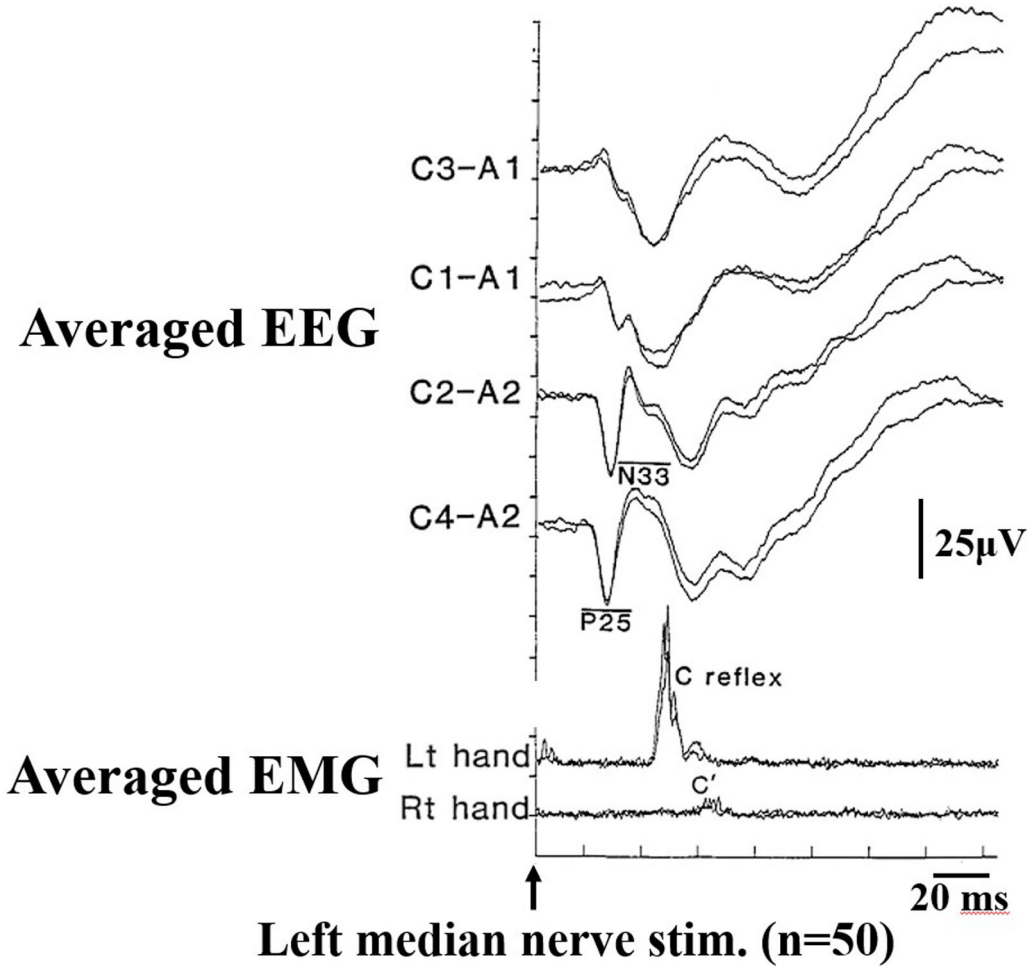

Figure 15.
Giant SEP (somatosensory evoked potential) and long-loop (C) reflex following electric stimulation of the left median nerve in a patient with progressive myoclonus epilepsy.

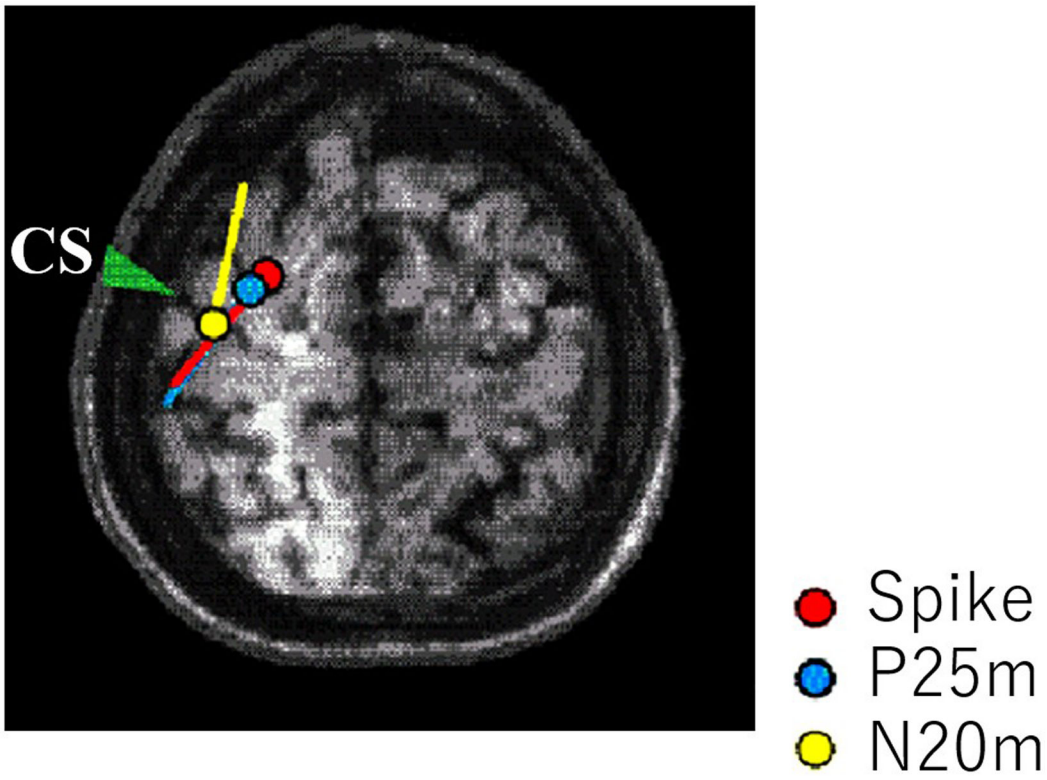

Figure 16.

Current dipoles of the early cortical components of the somatosensory evoked response to the median nerve stimulation, calculated from the averaged magnetic fields, in a patient with cortical reflex myoclonus. Note that the P25 peak of SEP (somatosensory evoked potential) (shown in blue) is generated in the precentral gyrus close to the spike preceding spontaneous myoclonus (shown in red) in the precentral gyrus. CS=central sulcus. (Courtesy of Dr. Tatsuya Mima, of Kyoto University Graduate School of Medicine, currently Ritsumeikan University, Kyoto)

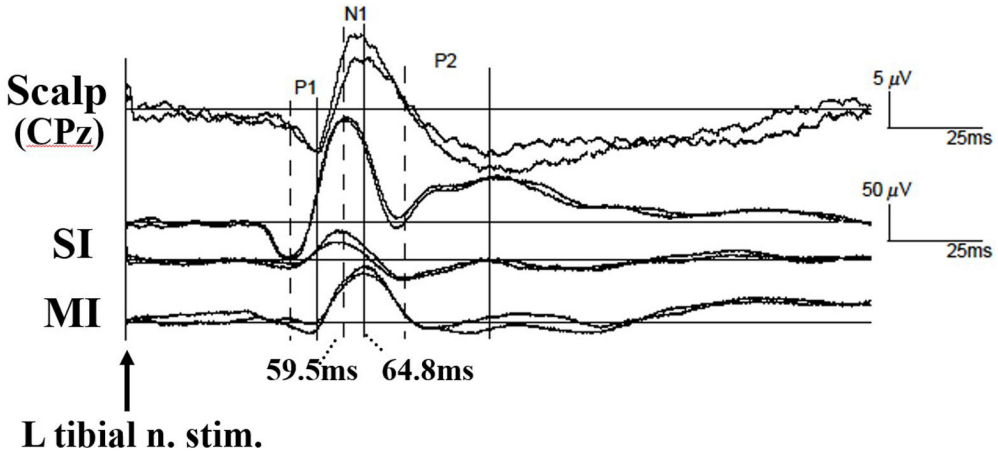

Figure 17.

Somatosensory evoked ECoG (electrocorticogram) following the left tibial nerve stimulation, recorded from the foot area of the right central sulcus in a patient with focal cortical reflex myoclonus of the left foot, investigated as a part of pre-surgical evaluation due to medically intractable epilepsy. The giant response is first seen in S1 (primary sensory cortex), 5 ms later followed by M1 (primary motor cortex). The scalp recording on the top trace shows the summation of the two responses. (From (Hitomi et al., 2006) with permission.)

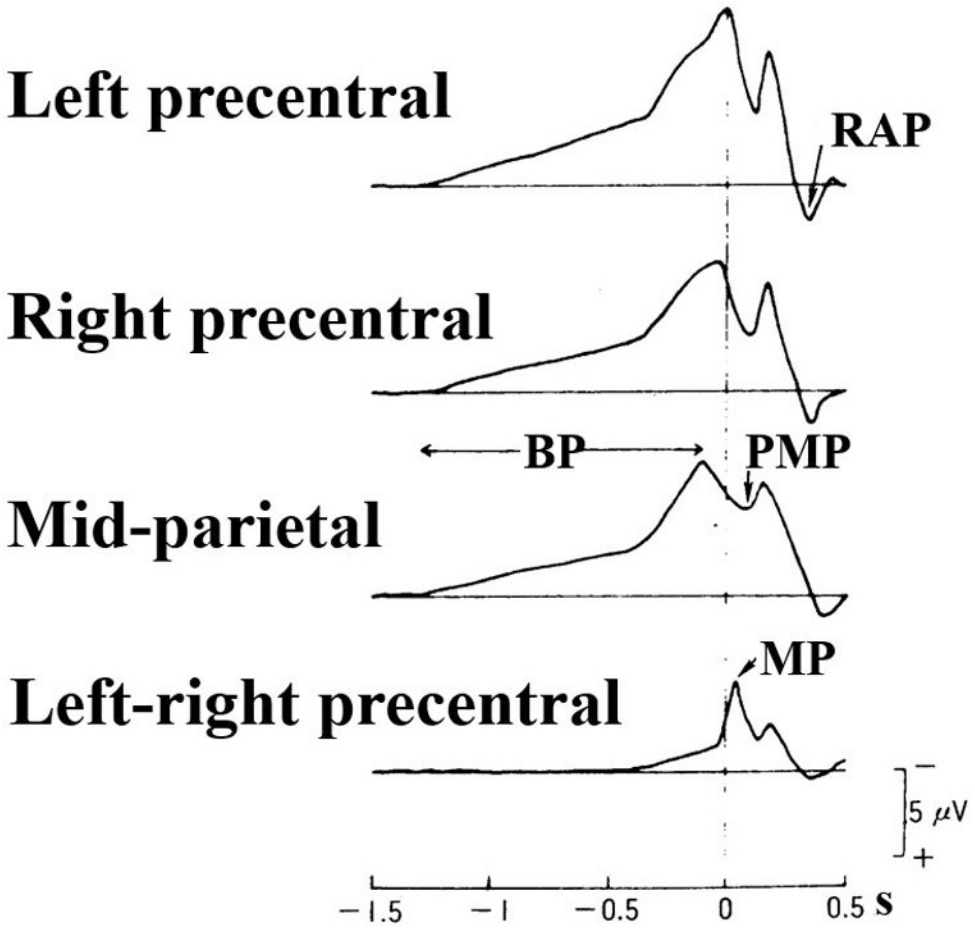

Figure 18.

Averaged EEGs time-locked to the self-paced movement of the right finger, originally reported by Kornhuber and Deecke (Kornhuber et al., 1965). EEG: electroencephalogram, BP: Bereitschaftspotential, PMP: pre-movement potential, MP: motor potential, RAP: reafferente Potentiale.

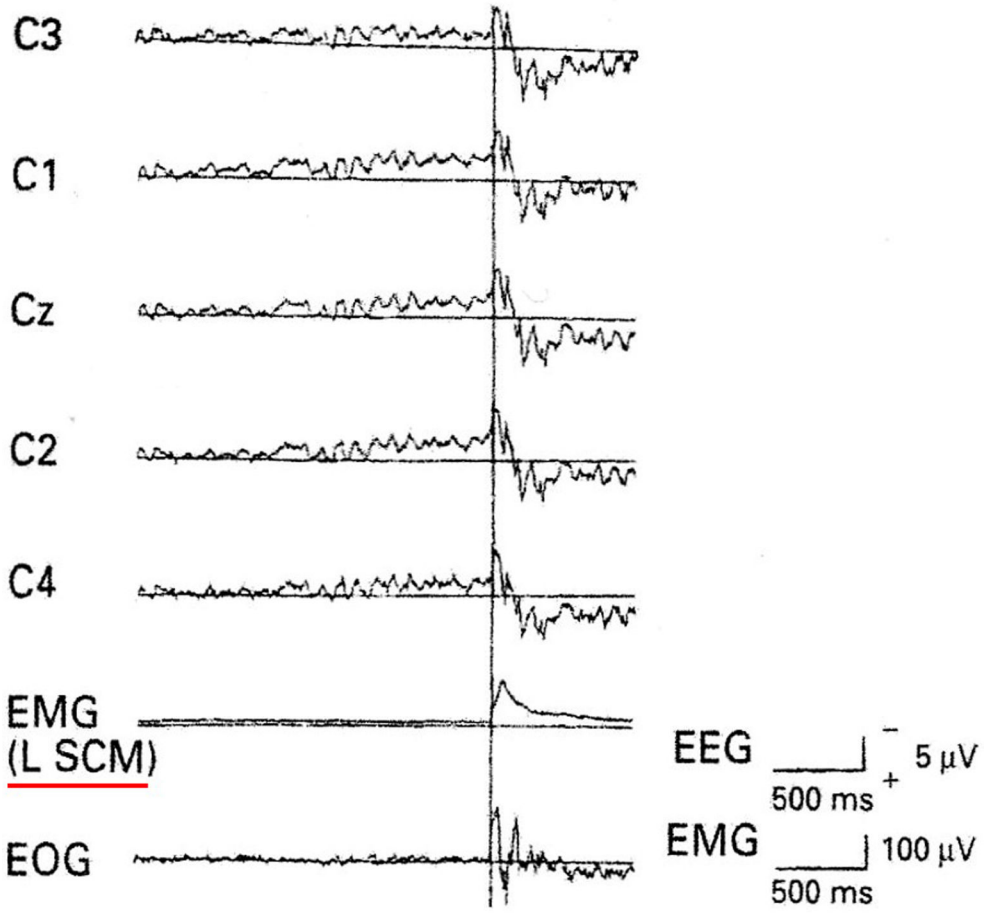

Figure 19.

Averaged EEG (electroencephalogram) time-locked to jerks of the neck which are clinically judged to be functional (psychogenic). A slowly rising, small, surface-negative potential is recognized at C1, Cz and C2 electrodes. EMG (electromyogram) was recorded from the left sternocleidomastoid (SCM) muscle. EOG=electro-oculogram. (From (Terada et al., 1995) with permission.)

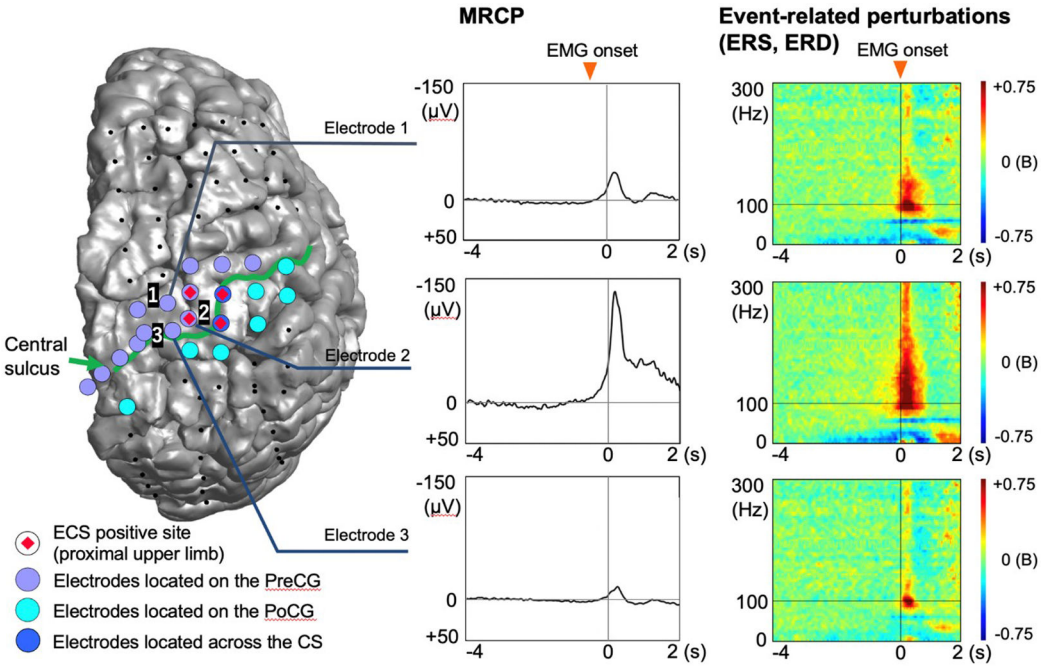

Figure 20.

Movement-related cortical potential (MRCP) and event-related perturbations recorded with subdural electrodes in a patient during self-paced movement of the left shoulder. Largest MRCP, event-related desynchronization (ERD) of the alpha and beta range and synchronization (ERS) of the high gamma range) are observed from Electrode 2 where high frequency stimulation elicited a positive motor response in the left shoulder. ECS=electrical cortical stimulation, CS=central sulcus, PreCG=pre-central gyrus, PoCG=post-central gyrus, EMG=electromyogram. (From (Neshige et al., 2018) with permission.)

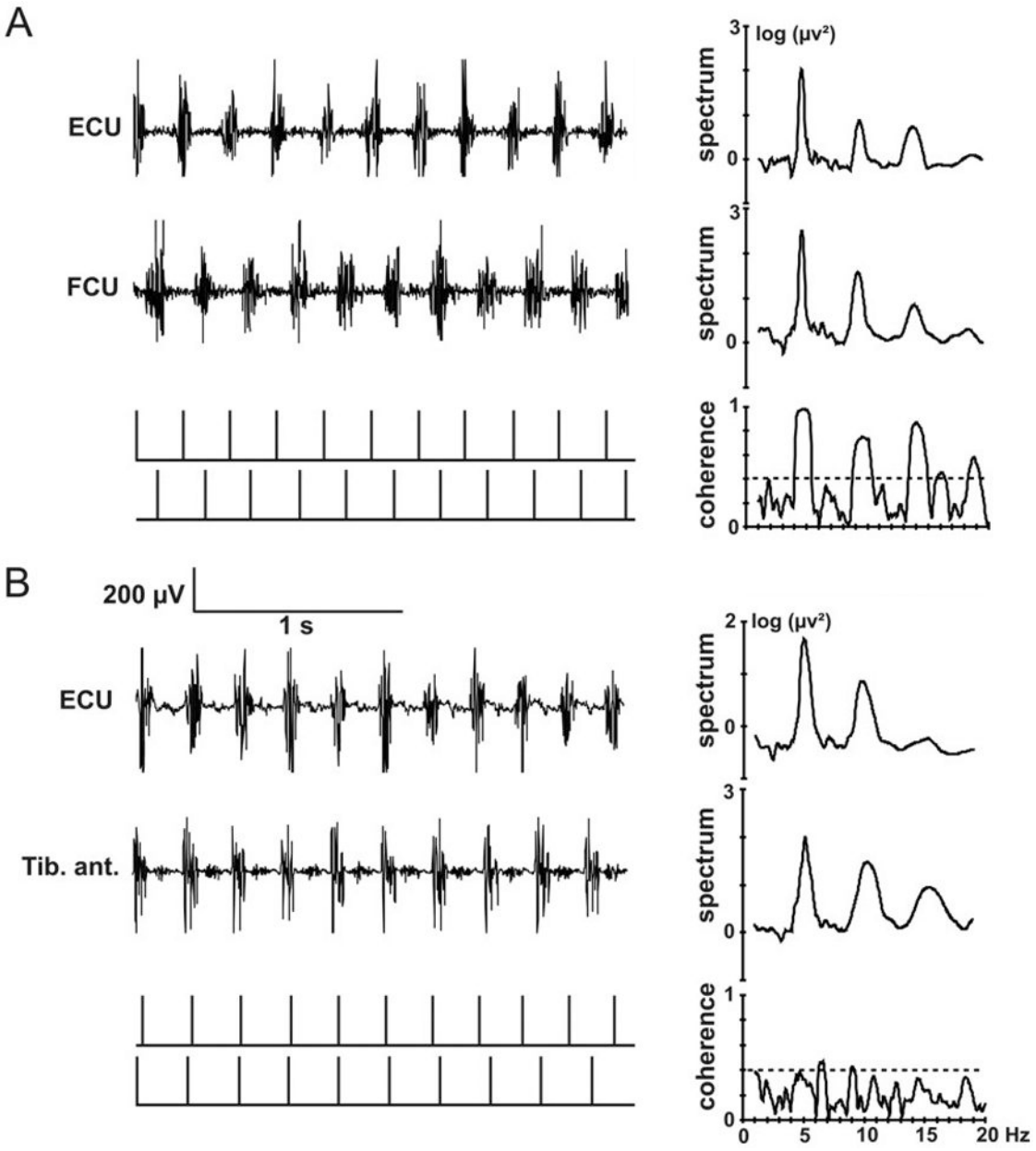

Figure 21.

EMG-EMG (electromyogram to electromyogram) coherence between muscles within the same limb (A) and between muscles from different limbs (B) in a patient with Parkinsonian tremor. Surface EMG recordings with tremor bursts and the time points of these bursts are displayed on the left, corresponding power spectra and coherence spectra on the right. Despite equal tremor frequencies in all recorded muscles, significant coherence is only found between muscles from the same limb whereas the oscillations in arm and leg are independent (not coherent). In the power spectra the lowest frequency peak is indicative of the tremor frequency; the higher frequency peaks are harmonics. ECU=extensor carpi ulnaris, FCU=flexor carpi ulnaris, tib ant=tibialis anterior.

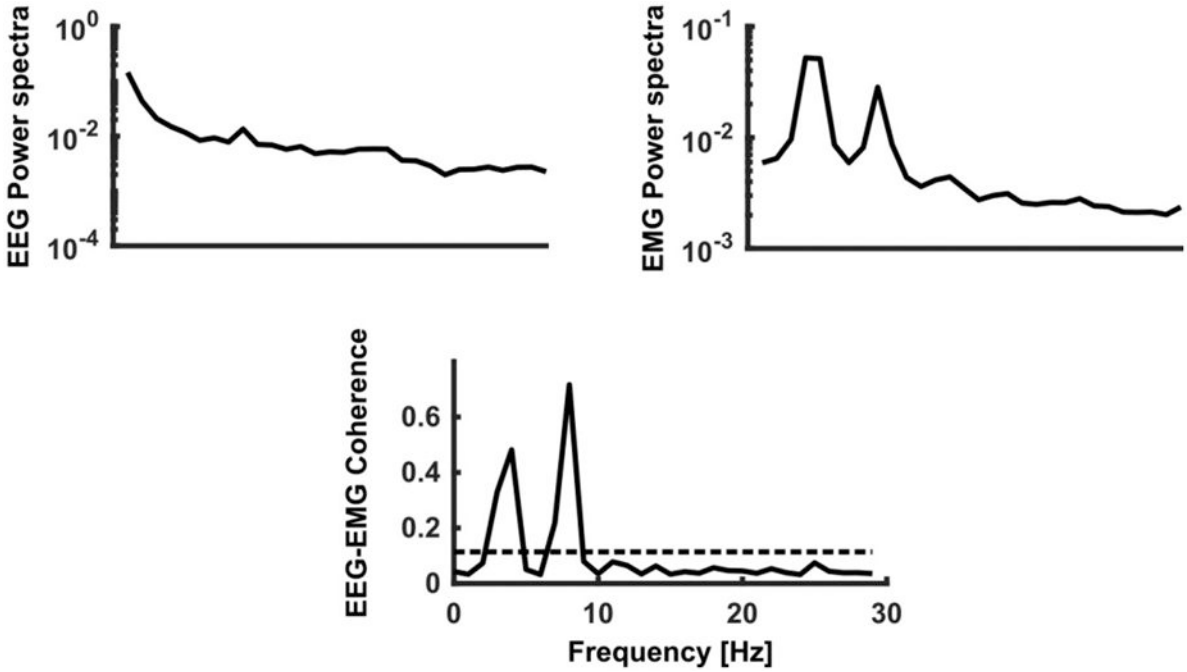

Figure 22.

Example of cortico-muscular coherence in an essential tremor patient with EEG (electroencephalogram) spectrum (Hjorth-transformed recording from C4) and EMG (electromyogram) spectrum (surface recording from left forearm extensors). Although not visible as a separate peak in the broad spectrum of the EEG significant coherence at the tremor frequency (and its first harmonic) reveals narrow-band oscillatory EEG activity related to contralateral tremor.

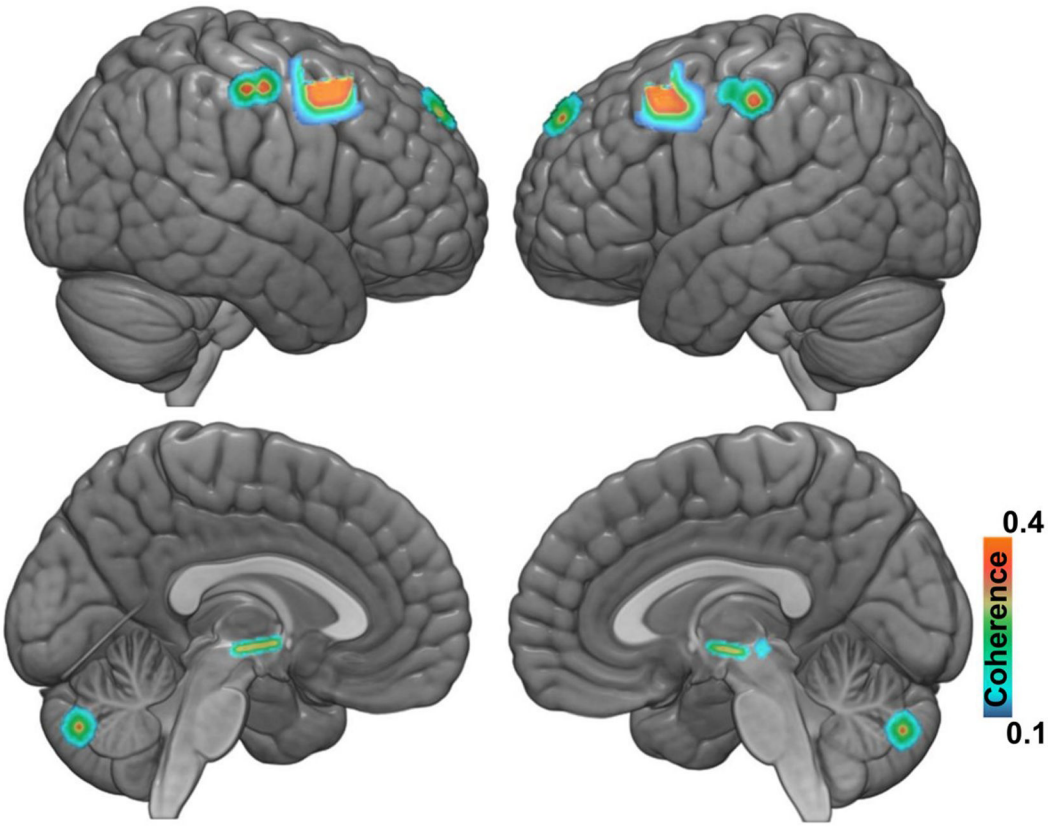

Figure 23.

Example of coherent sources in a template brain of a Parkinsonian tremor patient. The cortical sources are shown in the top of the figure for the left and right hemisphere. The bottom of the figure shows the subcortical sources for the left and right hemisphere separately. The marked brain regions contain signal that is coherent with the peripheral tremor at its frequency. In a further step the signal from these sources can be extracted to study the interaction within this tremor-related network. The color bar indicates the strength of coherence.

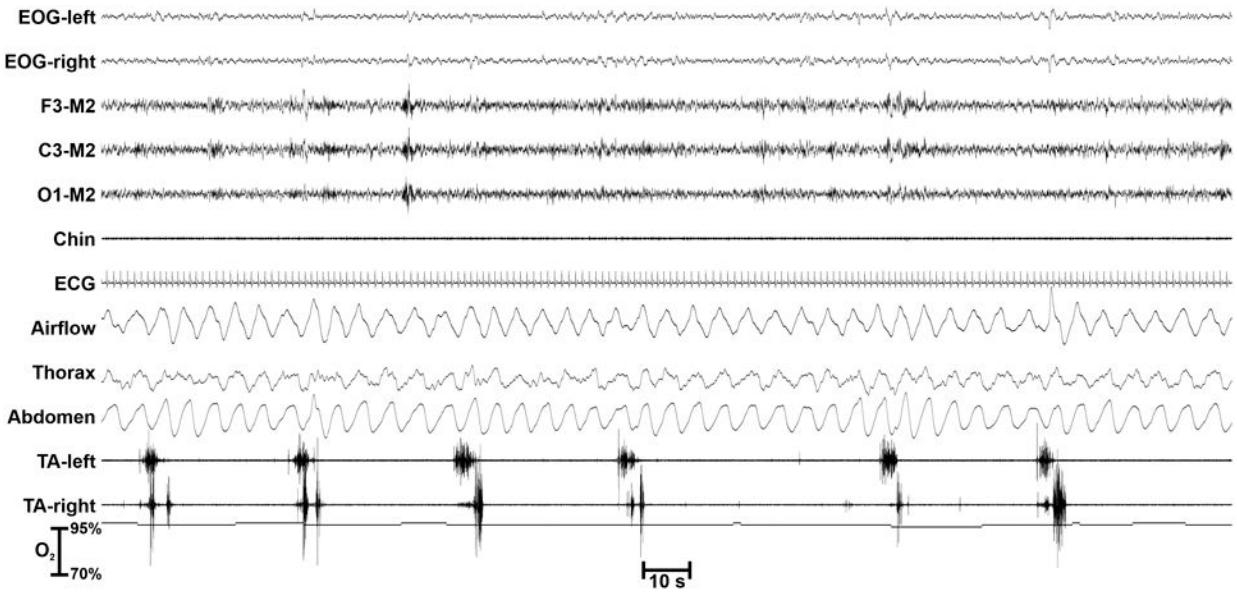

Figure 24.

Periodic leg movements during sleep stage N2 in a patient with RLS (restless legs syndrome) (TA = tibialis anterior, EOG=electro-oculogram, ECG=electrocardiogram).

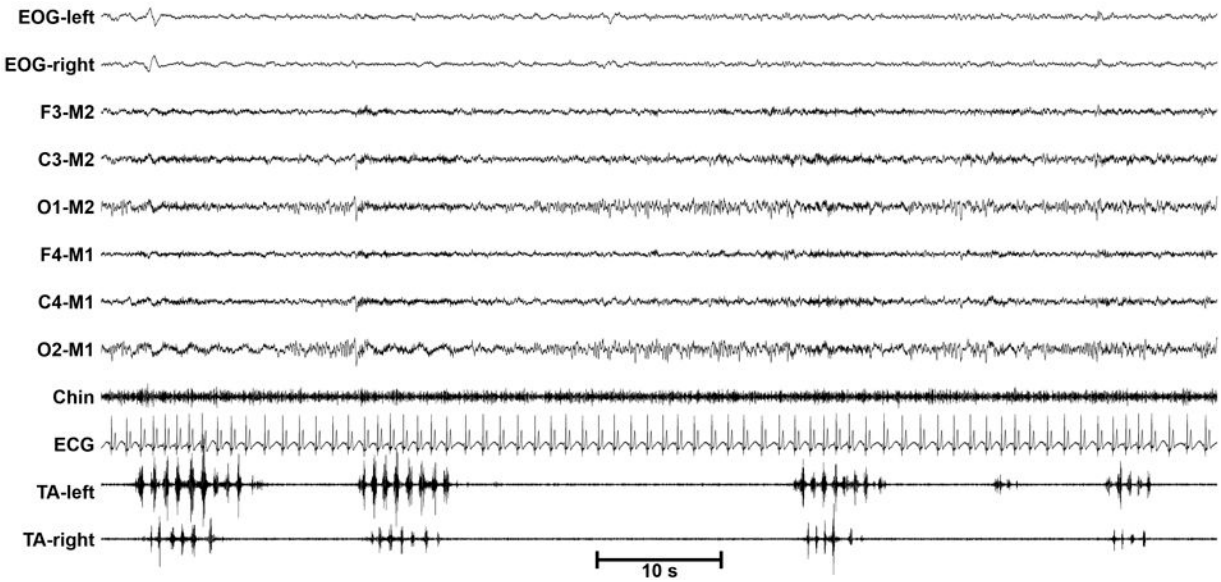

Figure 25.

Runs of alternating leg movement activity during light sleep in a patient with a complaint of daytime consequences (TA = tibialis anterior, EOG=electro-oculogram, ECG=electrocardiogram).

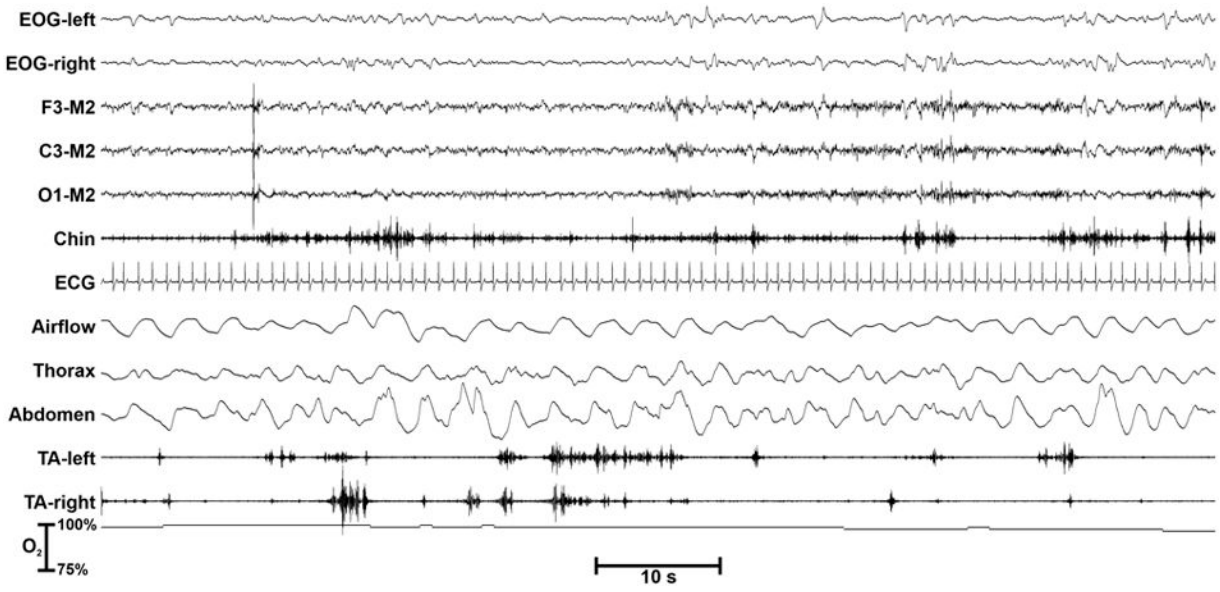

Figure 26.

REM (rapid eye movement) sleep without atonia in a patient with RBD (REM behavior disorder) (TA = tibialis anterior, EOG=electro-oculogram, ECG=electrocardiogram).

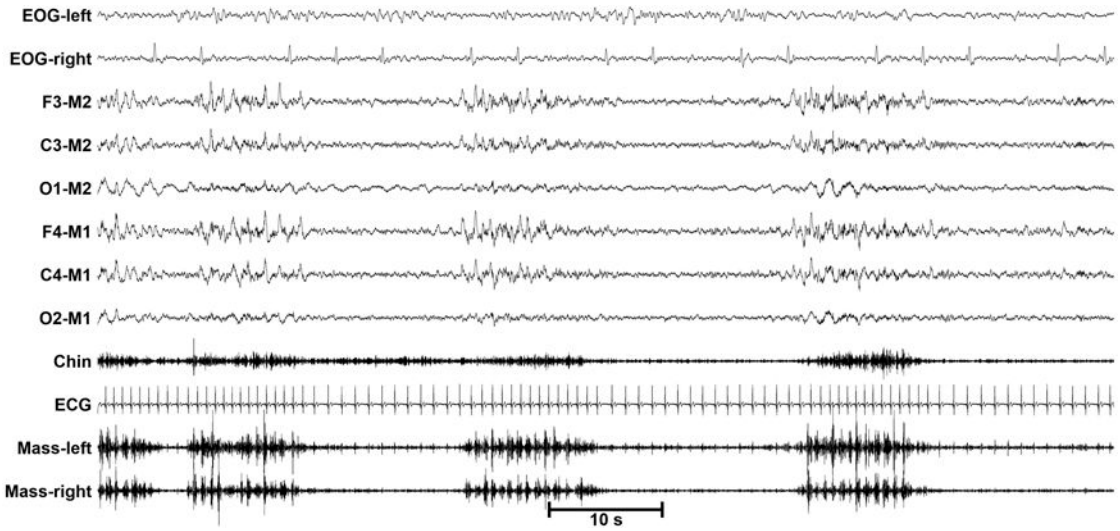

Figure 27.

Sequences of rhythmic masticatory muscle activations during light sleep in a patient with sleep bruxism (Mass. = masseter, EOG=electro-oculogram, ECG=electrocardiogram).

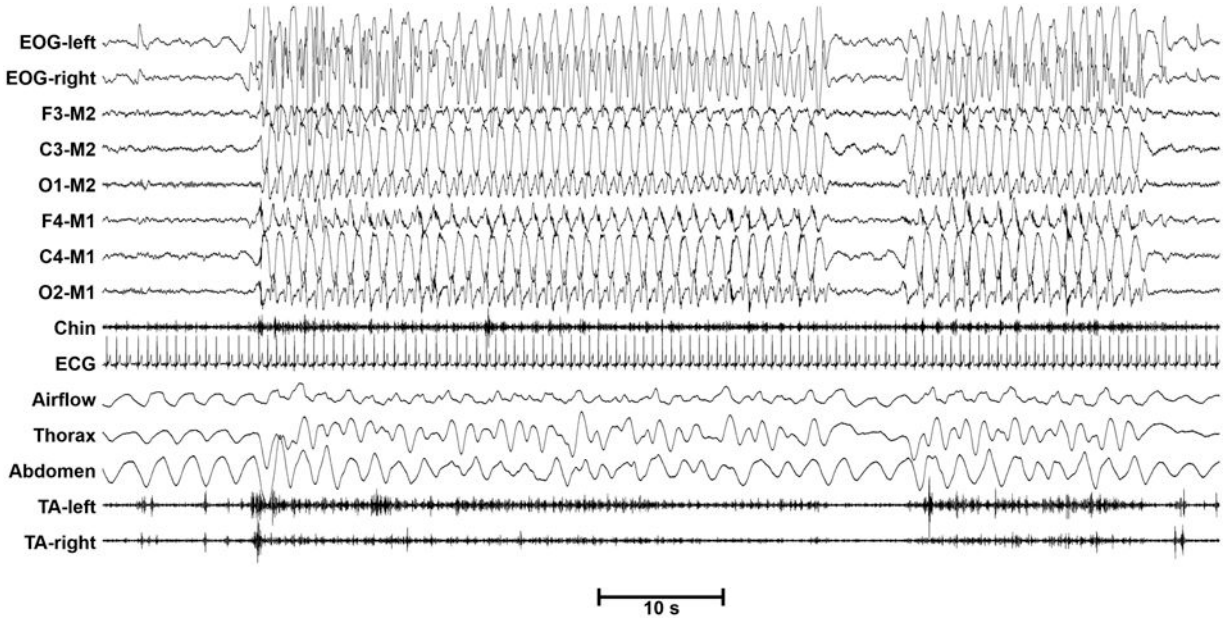

Figure 28.

Two episodes of rhythmic movements (head rolling) at the transition between wakefulness and sleep in a patient with RMD (Sleep Related Rhythmic Movement Disorder) (TA = tibialis anterior, EOG=electro-oculogram, ECG=electrocardiogram).

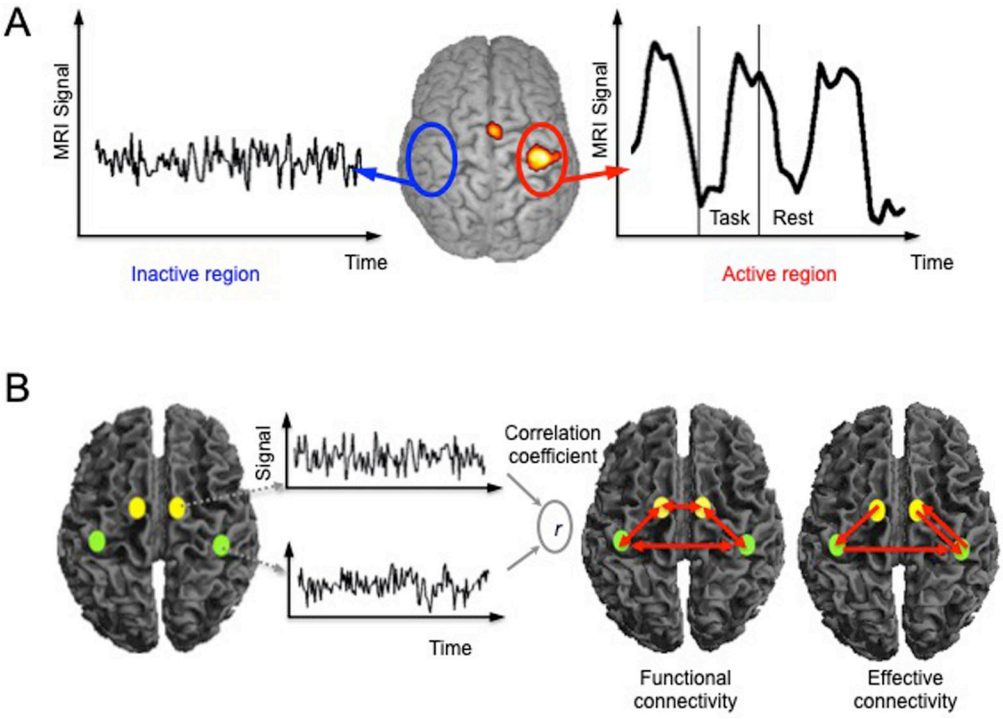

Figure 29.

A. Performing a task results in an increase in the MRI BOLD (Magnetic resonance imaging Blood Oxygen Level Dependent contrast) signal in the activated region (circled in red), here during hand movement. Signal increase begins one to two seconds after the onset of neuronal activity and peaks after 8 to 10 seconds after the onset of movement. When the subject stops working during the resting phase, the MRI signal gradually returns to the initial state. In the inactive region, signal changes are noise and do not correlate with the task. B. Functional connectivity between distant regions here in yellow and green is defined as the Pearson linear correlation coefficients ‘r’ between the BOLD fluctuations recorded in these two regions during rest or task performance (arrows). Effective connectivity quantifies the causal influence of a region on an adjacent region (oriented arrows).

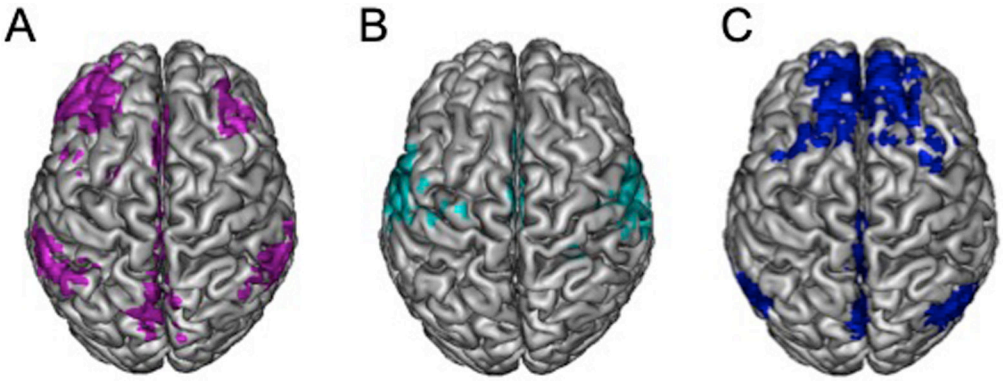

Figure 30.

Resting state networks are sets of distant regions in which BOLD(Blood Oxygen Level Dependent contrast) signal fluctuations co-vary with time at rest. Three networks are presented corresponding to the (A) fronto-executive, (B) motor, and (C) default mode network. The default mode network corresponds to a set of regions that are deactivated when performing goal directed tasks.

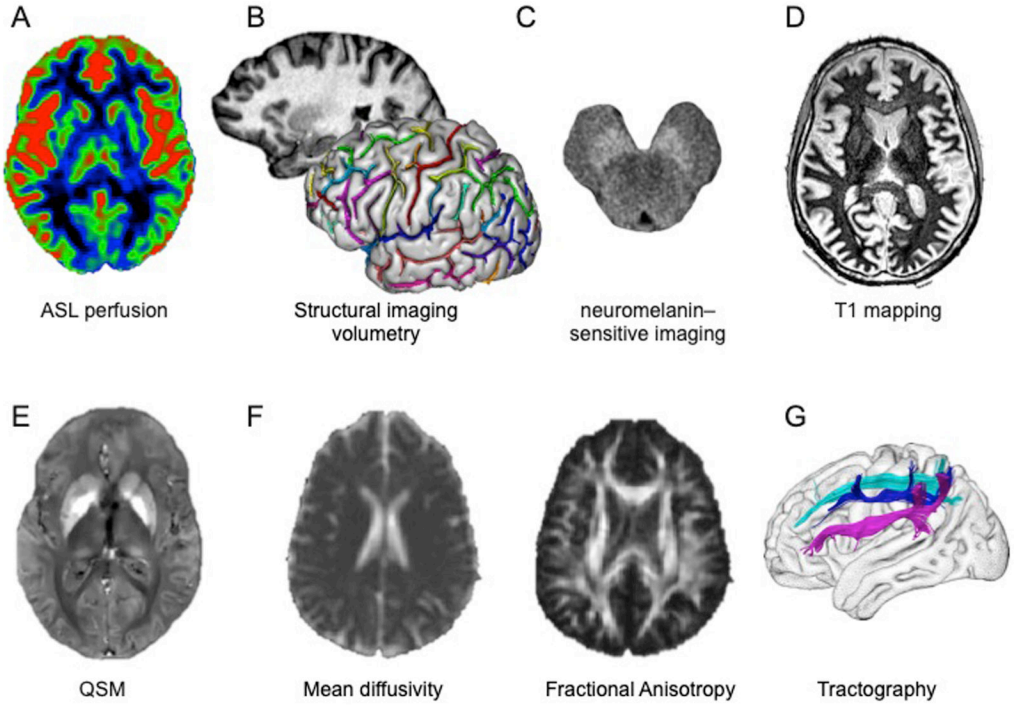

Figure 31.

Many other MRI (magnetic resonance imaging) techniques provide biomarkers that can be used to study the relationships between the motor system and the brain including (A) arterial spin-labeling (ASL) perfusion imaging, (B) structural imaging, (C) neuromelanin-sensitive imaging, a surrogate marker of dopaminergic neuron degeneration, (D) markers of tissue microstructure such as T1 mapping associated with myelination, (E) iron sensitive imaging (QSM=quantitative susceptibility mapping), and (F) diffusion imaging metrics including mean diffusivity (that quantifies the displacement of water molecules) and fractional anisotropy (that quantifies the directionality of water displacement). (G) Diffusion-based tractography provides indirect visualization and quantification of brain fiber tracts.

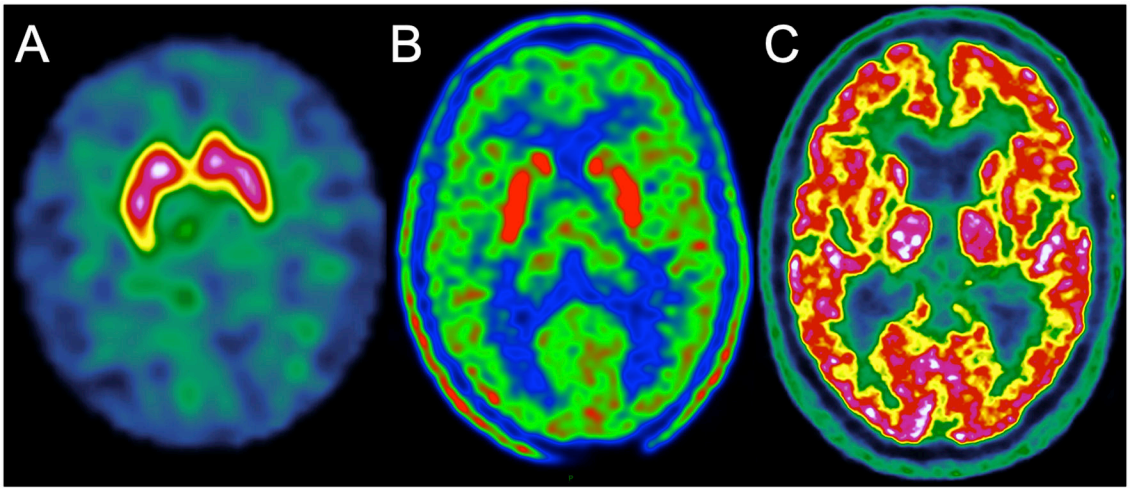

Figure 32.

Examination of dopaminergic function using (A) Single-Photon Emission Computed Tomography (SPECT) and 123I-FP-CIT (DaTSCAN ©) or (B) Positron Emission Tomography (PET) and 18F –DOPA. (C) Glucose metabolism is studied using 18F-fluorodesoxuglucose (18F-FDG).

Table 1.

EMG (electromyography) Appearance in Different Types of Involuntary Movements.

Disorder	EMG Pattern			Examples/comment
	10-50 ms, synchronous	50-100 ms alternating	100-300 ms	
Myoclonus	X			Epileptic myoclonus
		X		Ballistic movement overflow myoclonus
			X	Dystonic myoclonus
Tic		X	X	Not fully involuntary
Dystonia			X	Also athetosis
Chorea	X	X	X	Also dyskinesia, ballism

Table 2.

Generator sources of movement-related cortical potentials in unilateral simple hand movement. EMG = electromyography. (Cited from (Shibasaki et al., 2006).)

Component	Generator sources
Early BP	
Earliest	Pre-SMA (bilateral)
	SMA proper (bilateral) *
Next earliest	Area 6 (bilateral) *
Late BP (NS')	Area 6 (mainly contralateral) **
	Area 4 (mainly contralateral) **
MP (N-10)	Area 4 (contralateral) **
fpMP (N+50)	Area 3 (contralateral) **

* Somatotopically organized to some degree

** Somatotopicaly organized precisely

BP=Bereitschaftspotential, SMA=supplementary motor area, NS'=negative slope, MP=motor potential, fpMP=frontal peak of the motor potential