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# Overview of current diagnostic, prognostic, and therapeutic use of EEG and EEG-based markers of cognition, mental, and brain health

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## Abstract

The global burden of cognitive, mental, neurological, and substance-use disorders at 258 million disability adjusted life years calls for immediate "action" in their prevention and management. The electroencephalogram (EEG) is one of the most widely-used instruments for the non-invasive neuro-physiological measure of brain function and health. The EEG was originally used to solely monitor and record electric waves generated by electrical activity in the brain to aid in clinical decision-making and diagnosis. Technological improvements have made it possible for state-of the-art EEG computer-based systems like NeuralScan by Medeia Inc. to evaluate changes in power and in ratios of these brain waves with changes in brain and mental health status. Today's EEG machines can also identifying the precise localization of these changes enabling more accurate diagnosis and treatment. Improvements in EEG technology have made them robust, stationary/portable, high fidelity, versatile with the ability to carry out complex functions and calculations yet still be user/clinician-friendly highlighting their potential for use in clinical, research, epidemiological and public health settings. The present article presents an overview on EEG machines, their use in diagnosis, prognosis and therapy and to generate EEG-based markers in the area of cognition, mental and brain health.

## Introduction

### EEG in brain health and cognition

Normal functioning of the cerebral cortex is critical to physiological, neurological and mental health. Currently, cognitive, mental, neurological, and substance-use diseases/disorders account for 258 million disability adjusted life years (10.4% total all cause DALYS). This reiterates the need for better prevention, diagnostic and treatment options for brain health that can be used in clinical, epidemiological and public health settings [1-2]. Among the diagnostic and assessment tools for brain health are the a) non-invasive: neuro-clinical-physical examinations, questionnaires /instruments, electroencephalogram EEG, neuroimaging including **ultrasound,** magnetic resonance imaging, MRI, functional MRI (fMRI), **positron emission tomography** (PET), and computerized tomography (CT); and b) the invasive: biochemical tests, genetic tests, **cerebrospinal fluid (CSF) analysis, angiography, and b**iopsies. While the MRI, fMRI, PET and CT provide good spatial resolution of brain health, the EEG evaluates brain health via temporal resolution of brain function within the millisecond range [3-5], which is not possible with the other approaches. Due to its sensitivity to changes in brain function and structure and its simplicity of use in clinical settings, its use in intensive care has continued to increase in recent years [6-8].

The EEG assesses the neurophysiological aspects of brain function via the capture of the electric waves generated by electrical activity in the cerebral cortex. The cerebral cortex is divided into four lobes: the frontal, parietal, temporal and occipital; each of which performs specific functions. The 4mm thick cerebral cortex was mapped out by Brodmann based on cytoarchitecture, histology and function into 52 Brodmann's areas (BA). Twenty-six BA are of current interest in neuro-electrophysiological studies on brain and mental health. The normal brain waves emitted by the cerebral cortex based on their electrical activity are the Alpha (α) at 8-15 Hz, Beta (β) at 16-30 Hz, Gamma (γ) at 31-100 Hz with l*ow gamma at 30–70 Hz and high gamma at 70–150 Hz* and the Sensorimotor rhythm (SMR) at 13-15 Hz. The power and the ratio of these waves vary with regions of the cerebral cortex, the task at hand and different mental states. The morphology, power and ratio of these waves are used today to classify normal and abnormal brain function as well as in diagnosis, prognosis and therapy. Today's EEG machines allow precise localization of the normal/abnormal wave form in the brain and in turn which BA areas are involved enabling the clinical decision-making process.

### EEG as a diagnostic, prognostic and therapeutic tool

Indications for monitoring using EEG include seizure disorders such as epilepsy [9-13], traumatic brain injury [14-17], stroke [18-24], encephalitis [25-27], brain tumor [28], encephalopathy [29-31], memory problems [32-33], sleep disorders [34-35], coma [36-39],

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cardiac arrest [40], diagnosis of brain death [41-42] and dementia. In recent times EEGs have also been used to study Alzheimer's disease (AD) [43-44] and other forms of dementia [45-46], multiple sclerosis [47-49], pain disorders [50-51], Parkinson's disease [52-55], migraines [56-58], and behavioral disorders such as attention deficit hyperactivity disorder (ADHD) [59-61], autism [62-64], depression [65-67], post-traumatic stress disorder [68-71], complex developmental trauma disorder [72] and substance abuse [73-75]. With the advent of neurofeedback EEG became viable as a treatment option, being used for performance enhancement (academic, athletic or mental), and as treatment for ADHD, autism, Alzheimer's, post-traumatic disorders and substance abuse [76-80]. Thus since 1924 [81], the EEG has evolved from being an add-on tool in the diagnosis of brain health, to an instrument that is used for diagnosis, disease-staging [82-88], evaluation of prognosis including during the course of treatment (pharmacotherapy and chemotherapy) [89-93], and as itself as a therapeutic tool [76-80].

## EEG: Aiding diagnosis, preventing misdiagnosis and under-diagnosis

EEG has recently been used in the differential diagnosis of syndromes of uncertain etiology [94-97]. For example, subcortical ischemia or multiple infarcts or single strokes have been known to cause personality changes, affective disorders, and even psychosis. Similarly, psychiatric disorders such as obsessive compulsive disorder (OCD), schizophrenia, autism, dyslexia, and addictions have shown distinct differences in neurological features between subjects and controls. The EEG is also useful in distinguishing diseases with similar symptoms yet different etiopathophysiology. Cognitive impairments, for example, can be due to a range of reasons like electrolyte imbalance, hypoglycemia, sleep disorders, stress, head injury, pain, dementia, etc. [94].

Recently the EEG's potential to generate either early diagnostic markers or biomarkers has been explored for neurological disorders like AD [43-44], multiple sclerosis [47-49], Parkinson's disease [52-55], schizophrenia [98], autism [62-64], and dyslexia. A study on neurodegeneration and progression from mild cognitive impairment (MCI) to fully developed AD revealed significantly higher levels of delta bands among AD subjects, for example [84]. A 2-year longitudinal study on 86 MCI patients used six EEG biomarkers to successfully predict the conversion of 25 patients exhibiting beta activity to AD with 88% sensitivity and 82% specificity [86]. Automatic feature extraction techniques helped predict focal seizures increasing the sensitivity to 87.8% [88].

## Current EEG technology in a nutshell

The design, specification, maintenance and calibration protocols for electrodes [99-109], electrode placement systems [109-118], use of ground and reference electrodes, EEG machines (analog, digital or multi-channel), EEG calibrators and montages [119] are governed by stringent standards and guidelines [120-129]. EEG recording procedures are categorized into two stages: a) data acquisition and pre-processing, and b) feature extraction. The stages are performed as follows:

*Acquisition and pre-processing:* The EEG captures the pyramidal neuronal activity comprising action potentials (3ms) and postsynaptic potentials (200ms) via electrodes following an excitatory stimulus [98]. The 20μV signal is amplified using a differential amplifier, followed by normal amplifiers. High-pass (HPF), low-pass (LPF) and notch filters are then used to minimize/overcome/nullify "noise" arising from intrinsic and extrinsic factors, and the distortion caused by aliasing when the analog signal is digitized by the analog-to-digital converter [122-128].

*Artifact correction:* Correction for artifact removal or attenuation is carried out depending on the data and study design. Artifacts due to eye blinks or head shaking which are symptoms are attenuated and not removed. ICA (Independent Component Analysis) and SSP (Signal Space Projection) are some of the methods used for artifact attenuation [130-133]. Signal averaging, thresholding of the output, signal enhancement, and finally edge detection are then carried out.

*Data processing:* Processing of data includes feature extraction, selection and classification. In general for most digital EEG machines, feature extraction alone is carried out. Fast Fourier Transform (FFT), Wavelet Transform (WT), Time-Frequency Distributions (TFD), and Foreword and Inverse Source Space analysis are among the methods used for feature extraction [133-137]. Patient data is then stored for neuroclinical assessment and report generation [138-140].

## Software developments in EEG technology

Previously, the patterns of EEG wave forms/wave morphology alone were used in combination with other neurological tests to diagnose neurological disorders [141-143]. In more recent years the processed EEG data (wave forms) are quantified via quantitative EEG (q-EEG), wherein a specialized software program converts 1-dimensional (1-D) brain wave signals into 2-D topographical color maps comparing a patient's brain function to a normative database (Neuroguide, FDA research standard) [144-146]. The resulting color code allows for the generation of quantitatively relevant Z-scores. Another software development that revolutionized the field improving the spatial resolution of EEGs was the use of Independent Component Analysis (ICA) in combination with Low Resolution Electromagnetic Tomography (LORETA) [145-153] to transform 2-D into 3-D EEG data, which enabled locating the source of EEG waves on the cortical lobes. Source location (originally only possible via CT or MRI) is important as it enables identification of the functional regions involved in specific responses or disease states.

Figure 1 shows the components of the **NeuralScan** by Medeia a state-of the-art EEG computer-based system. It is in keeping with current standards and incorporates the most up-to-date technological improvements in the field of EEG machines. Figure 1A shows the 21-channel EEG cap. The built-in software can carry out routine clinical assessment of EEG wave forms (alpha, beta, theta or gamma) and wave forms tests, namely; resting-state EEG (eyes closed and opened). Or, the system can evaluate working memory and ERPs (Figure 1B) from evoked potentials (visual, auditory, odd ball paradigm) and behavioral motor tests. The system is capable of i) "automatic" artifact (blinks, pulse artifact, MR gradient artifact, ballisto-cardiogram, and bad blocks) removal via FFT, wavelet and ICA as well as ii) feature extraction, iii) frequency-based analysis of the EEG wave forms and iv) for transformation from the time domain to the frequency domain. The software can also perform qEEG for brain mapping, power and frequency analysis and comparison with a normative database provided with the package (Figure 1C) and with eLORETA to carry out source analysis (Figure 1D). Also provided with it is a neuropsychological questionnaire with some sections that the patient answers (self-reporting) and others that the clinician administers. The test takes in total 15 minutes to perform. The reporting system can be customized to make summarized reports that can be easily understood by physician and patient (Figure 1E), or detailed reports that can depict correspondence of EEG and vital signs (Figure 1F).

## EEG-based markers of cognition, mental and brain health

Normal EEG wave forms [154-156] vary with age, mental states and depending on if they are stimulus induced or resting-state. Abnormal wave form patterns [126,157] are subdivided into epileptic and generalized non-ictal wave forms and include: intermittent slowing, intermittent rhythmic delta activity (IRDA) continuous slow activity (diffuse slowing, alpha coma), periodic abnormalities (Burst suppression, periodic discharges (GPDs/SIRPIDS), and background suppression. Disease-specific patterns are also observed. For example, disease-specific EEG patterns have been noted in subacute sclerosing panencephalitis (SSPE) [158] and in Creutzfeldt-Jakob disease [159].

The processed EEG wave forms captured at a) resting-state EEG (eyes closed and opened), b) following a specific task (working memory) and c) event related potentials (ERPs) including evoked potentials (visual, auditory, odd ball paradigm) are the source of several brain health biomarkers [160-162]. Figure 1 summarizes wave types that can be used in EEG to provide information on neurological and mental health EEG-generated markers that have been used in both neurological/mental health research and for clinical assessment.

## Event related potentials (ERPs) in disease and research

Evoked or event-related potentials (ERPs) are obtained following an event/stimulus. The stimulus can be visual, auditory, motor or task related. Checker-boards with black and white squares with the black and white squares alternating their positions at a predefined period are often used as visual stimuli. They are presented on a computer screen for a specified duration, and as the brain is able to recognize the interchange in black and white squares within a fraction of a second; this recognition is captured in an EEG wave form. The epochs that capture one complete stimuli and response cycle are marked out and selected. As the stimulus/test duration may be 5 minutes. All the epochs pertinent to that duration and stimulus are similarly marked and selected. The averaged response to a particular stimulus provides the event-related potential (Figure 1D) for that stimulus. The ERP waveform has both positive and negative components which are denoted as "P" and "N"

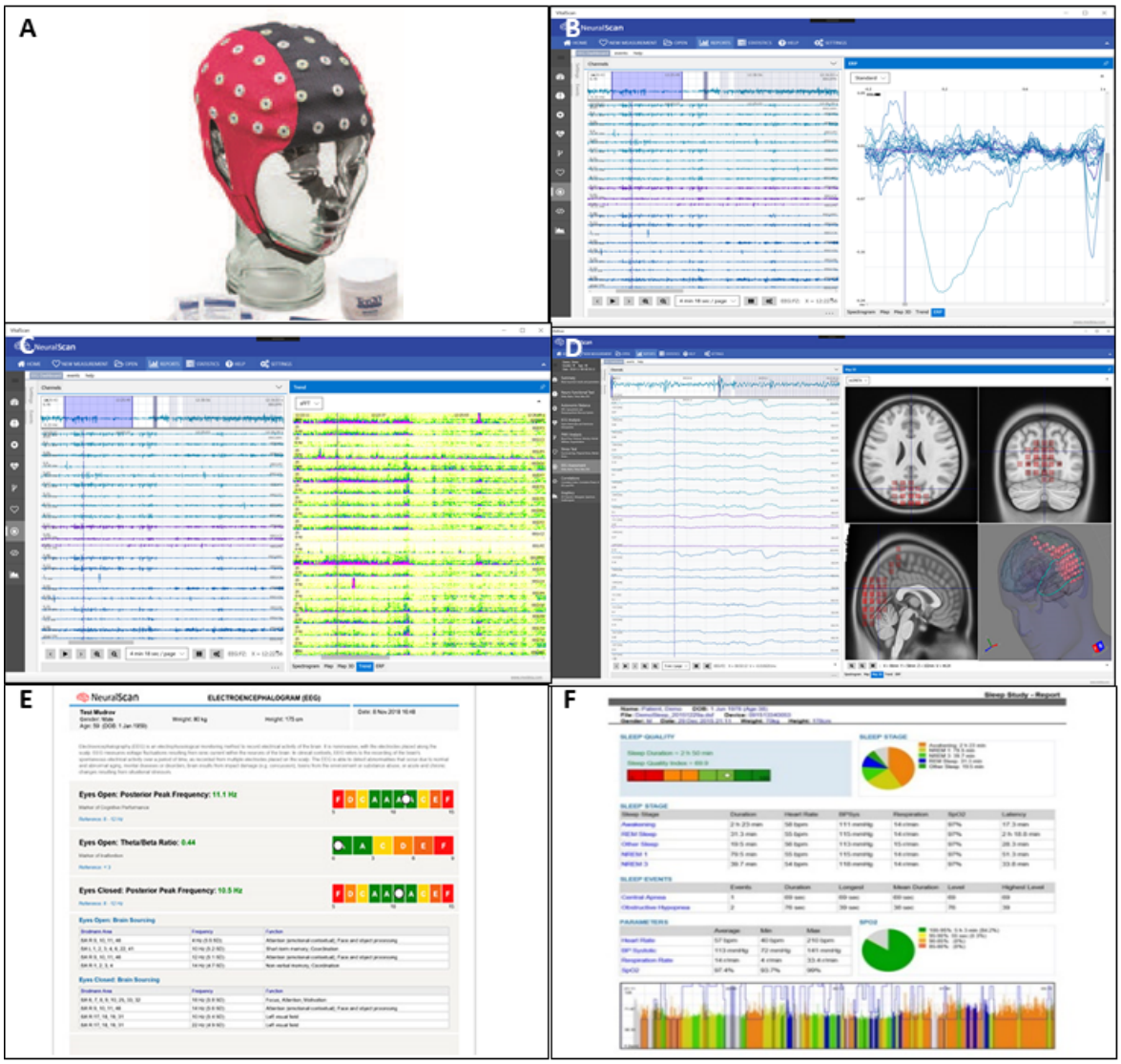


**Figure 1.** Components of Neuralscan by Medeia. (A) 21-Channel electroencephalograph (EEG) cap; (B) Signal averaging for event related potentials (ERP) generation; (C) Power analysis, frequency analysis, and QEEG mapping; (D) Source localization via exact low-resolution electromagnetic tomography (eLORETA); (E) simple report; (F) full report with time correspondence to vital signs reading

respectively with a number (P100 and N100) that either indicates the latency in milliseconds or the hierarchical position of the wave form.

In an ERP study of schizophrenic patients, P100 amplitude principal component analysis revealed that while the first principal component (global activity) and the second (reciprocal anterior-posterior activation) were similar in patients and controls, the third component (hemispheric reciprocity in activity) showed unique activation of the center versus anterior and posterior regions in patients with schizophrenia [163]. In a study on Autism Spectrum Disorder (ASD), autistic children exhibited longer P100 latencies, weaker N100 amplitudes and larger P300 amplitudes compared with typically developing (TD) children. [164]. ERPs detected in the early phase following traumatic brain injury have been found to serve as predictive markers for functional and cognitive recovery at six months post-injury [165]. ERPs have also been used to identify impairment in the dorsolateral prefrontal and anterior cingulate cortices in Parkinson's Disease [166]. EEG (non-linear complexity) in combination with a neuropsychological assessment (Alzheimer's Disease Assessment Scale-cognitive: ADAS-Cog) and cardiovascular history assessment was also found to increase diagnostic accuracy from 80% to 92% for distinguishing between AD, vascular dementia, mixed dementia, and MCI [82].

Specific cortical auditory evoked ERPs have also been used to identify sensitive period cutoffs for primary auditory cortical development in juvenile cochlear implant recipients [167]. Further, ERPs have been used to identify differential emotional processing based on responses to emotionally negative stimuli in veterans with PTSD [168]. A study of African American seniors has also found that EEG spectral power at rest with eyes closed during a One Card Back Learning test (OCL, memory) was able to differentiate those at-risk of MCI from those that were stable [32].

## Technological variants of EEG

In more recent years, specialized types of EEG have been developed for specific functions. Each of these provide unique advantages for applications in research or in the clinic. This section discusses two of the most common of these recent EEG-based technologies, quantitative EEG and low resolution electromagnetic tomography. (Table 1).

## Quantitative EEG (qEEG)

In Quantitative EEG (qEEG), EEG data is used to create 2-D topographical color-coded brain maps that reflect the Z-scores obtained of the patient's brain functioning when compared to a normative reference database (Neuroguide, FDA research standard) (Figure 1C). The waves are then analyzed to determine their distribution, power, ratio, coherence and connectivity across the cerebral lobes [144-146]. A study on the use of qEEG to monitor and aid in the treatment of traumatic brain injury (TBI) confirmed that alpha power (AUC=0.87, $p<0.01$) and variability of the relative fast theta power (AUC=0.84, $p<0.01$) demonstrated high prognostic value [17]. qEEG was also shown to have clinical diagnostic value for viral encephalitis, exhibiting a higher level of detail and precision compared with EEG [27]. Unusually high theta activity in the frontal region and higher theta-to-beta activity is observed in ADHD [169]. A review of studies on Parkinson's disease (PD) found slowing EEG frequencies to be correlated with a decline of cognition with increase of spectral powers in delta and theta and a decrease in alpha, beta, and gamma activity in this disease setting. Topographically the occipital, parietal, and temporal lobes also showed higher correlation with the spectral changes observed in Parkinson's disease [170].

## Low resolution electromagnetic tomography (LORETA)

In Low Resolution Electromagnetic Tomography (LORETA), [147-153] 2-D EEG data is converted into 3-D data to locate the

**Table 1.** EEG-based markers of brain/mental health

| | |
|---|---|
| **EEG** | • Wave form characteristics<br>• Peak frequency of the brain waves recorded<br>• Theta-Beta Power Ratio<br>• Clinical significance/relevance of a) Low peak frequency, b) High peak frequency |
| **Evoked Potentials & Event-related potentials (ERPs)** | • Visual evoked potentials (VEP), Auditory evoked potentials<br>• ERPs their mean and peak amplitude and latency across neuro- and mental disorders.<br>• Potential ERP based Brain Biomarkers: C1 and P1, P200, P300, P3a, P3b, P600, N100, N200, N2pc, N170, N400, Early left anterior negativity (ELAN). Error-related negativity (ERN), Late positive component (LPC), Lateralized readiness potential (LRP), Mismatch negativity, N2pc, Bereitschaft's potential, Contingent negative variation (CNV), Somatosensory evoked potential, Visual N1, ERP synchrony and ERP desynchrony.<br>• Odd ball paradigm, ERP: the P300 and the latency (in ms)<br>• Steady-state visual evoked potentials (SSVEPs), the brain responses to repetitive visual stimulation (RVS),<br>• Resting state EEG |
| **Frequency Analysis & qEEG** | • Absolute power (voltage, $P=mV^2$) in the patient's EEG database<br>• Relative power in a brain wave compared to the total power in a patient's EEG ($\theta/ \theta + \beta + \alpha + \Delta$)<br>• Inter- and intra-hemisphere coherence, right-left hemisphere and front-back balance in power and symmetry<br>• Ratios of the EEG brain waves (Hz) and their influence on brain and mental health?<br>• Mean frequency of the patient's brain waves.<br>• Z-score value of the patient's raw scores compared with the normative database – their direction and magnitude of the difference and their implications on brain health<br>• Appearance of the above variables if there is a local, focal, regional or generalized abnormality? |
| **sLORETA & eLORETA** | • Source of the electrical activity from the electrode/channel/derivation located in the brain<br>• Which Brodmann areas in the brain are involved?<br>• What are their cytoarchitecture, histology and function? |

source of the EEG waves on the cortical lobes. This in turn identifies the functional areas involved, localizing wave responses to the source to provide a neuroanatomical context (Figure 1D).

In a case study of ADHD investigating treatment with dopamine agonist KB200z, LORETA was used to successfully identify increased in frequency bands in the anterior, dorsal and posterior cingulate regions and right dorsolateral prefrontal cortex in response to treatment. Another study used LORETA to demonstrate increased dissociation between brain processes in schizophrenic patients, a key factor thought to account for the differences in the cognitive and emotional state of schizophrenic patients [98]. Specific LORETA parameters (current phase density and lagged phase synchronization) have also been successfully correlated with Aβ42 and total tau concentration in Alzheimer's disease patients. A LORETA z-score feedback approach has also been shown to reduce pain in head and neck cancer patients, improvements associated with modified brain activity in pain-associated brain regions. In another study comparing healthy individuals with patients with treated and untreated menopausal syndrome and depression, LORETA was used to successfully identify cortical anatomical correlates of depression as well as the pharmacotherapy mode of action. LORETA was also able to identify significant elevations in alpha activity in the precuneus, and posterior middle temporal gyrus and decreased alpha activity in the medial frontal cortex, including the anterior cingulate and the superior and medial frontal gyri, in migraine patients.

## Conclusion

The EEG has evolved in recent decades from a noninvasive monitoring tool into an instrument with diagnostic, prognostic and therapeutic/neurofeedback applications for neurological and mental disorders. Today's state-of-the-art EEG machines allow for spectral analysis using qEEG, and source analysis using LORETA. EEG-based technologies have also proven useful in the diagnosis of disorders with complex etiology and in the early diagnosis of cognitive impairment, providing clinicians with a valuable window of opportunity to implement preventive measures via lifestyle changes and/or therapeutic interventions. Today's state-of-the-art EEG machines, like NeuralScan by Medeia can perform tests with high accuracy within 15 minutes. Portability of current EEG machines allow for ease-of-use in public health and laboratory settings, as well as for research purposes and clinical use.

## Authorship and contributions

PM, CC, JL, MA, and SD all contributed equally to the writing, review, and approval of this manuscript.

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## Conflicts of interest

One author is employed by Medeia, Inc. that produces NeuralScan.

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# Overview of current diagnostic, prognostic, and therapeutic use of EEG and EEG-based markers of cognition, mental, and brain health

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## Abstract

The global burden of cognitive, mental, neurological, and substance-use disorders at 258 million disability adjusted life years calls for immediate "action" in their prevention and management. The electroencephalogram (EEG) is one of the most widely-used instruments for the non-invasive neuro-physiological measure of brain function and health. The EEG was originally used to solely monitor and record electric waves generated by electrical activity in the brain to aid in clinical decision-making and diagnosis. Technological improvements have made it possible for state-of the-art EEG computer-based systems like NeuralScan by Medeia Inc. to evaluate changes in power and in ratios of these brain waves with changes in brain and mental health status. Today's EEG machines can also identifying the precise localization of these changes enabling more accurate diagnosis and treatment. Improvements in EEG technology have made them robust, stationary/portable, high fidelity, versatile with the ability to carry out complex functions and calculations yet still be user/clinician-friendly highlighting their potential for use in clinical, research, epidemiological and public health settings. The present article presents an overview on EEG machines, their use in diagnosis, prognosis and therapy and to generate EEG-based markers in the area of cognition, mental and brain health.

## Introduction

### EEG in brain health and cognition

Normal functioning of the cerebral cortex is critical to physiological, neurological and mental health. Currently, cognitive, mental, neurological, and substance-use diseases/disorders account for 258 million disability adjusted life years (10.4% total all cause DALYS). This reiterates the need for better prevention, diagnostic and treatment options for brain health that can be used in clinical, epidemiological and public health settings [1-2]. Among the diagnostic and assessment tools for brain health are the a) non-invasive: neuro-clinical-physical examinations, questionnaires /instruments, electroencephalogram EEG, neuroimaging including **ultrasound,** magnetic resonance imaging, MRI, functional MRI (fMRI), **positron emission tomography** (PET), and computerized tomography (CT); and b) the invasive: biochemical tests, genetic tests, **cerebrospinal fluid (CSF) analysis, angiography, and b**iopsies. While the MRI, fMRI, PET and CT provide good spatial resolution of brain health, the EEG evaluates brain health via temporal resolution of brain function within the millisecond range [3-5], which is not possible with the other approaches. Due to its sensitivity to changes in brain function and structure and its simplicity of use in clinical settings, its use in intensive care has continued to increase in recent years [6-8].

The EEG assesses the neurophysiological aspects of brain function via the capture of the electric waves generated by electrical activity in the cerebral cortex. The cerebral cortex is divided into four lobes: the frontal, parietal, temporal and occipital; each of which performs specific functions. The 4mm thick cerebral cortex was mapped out by Brodmann based on cytoarchitecture, histology and function into 52 Brodmann's areas (BA). Twenty-six BA are of current interest in neuro-electrophysiological studies on brain and mental health. The normal brain waves emitted by the cerebral cortex based on their electrical activity are the Alpha (α) at 8-15 Hz, Beta (β) at 16-30 Hz, Gamma (γ) at 31-100 Hz with l*ow gamma at 30–70 Hz and high gamma at 70–150 Hz* and the Sensorimotor rhythm (SMR) at 13-15 Hz. The power and the ratio of these waves vary with regions of the cerebral cortex, the task at hand and different mental states. The morphology, power and ratio of these waves are used today to classify normal and abnormal brain function as well as in diagnosis, prognosis and therapy. Today's EEG machines allow precise localization of the normal/abnormal wave form in the brain and in turn which BA areas are involved enabling the clinical decision-making process.

### EEG as a diagnostic, prognostic and therapeutic tool

Indications for monitoring using EEG include seizure disorders such as epilepsy [9-13], traumatic brain injury [14-17], stroke [18-24], encephalitis [25-27], brain tumor [28], encephalopathy [29-31], memory problems [32-33], sleep disorders [34-35], coma [36-39],

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cardiac arrest [40], diagnosis of brain death [41-42] and dementia. In recent times EEGs have also been used to study Alzheimer's disease (AD) [43-44] and other forms of dementia [45-46], multiple sclerosis [47-49], pain disorders [50-51], Parkinson's disease [52-55], migraines [56-58], and behavioral disorders such as attention deficit hyperactivity disorder (ADHD) [59-61], autism [62-64], depression [65-67], post-traumatic stress disorder [68-71], complex developmental trauma disorder [72] and substance abuse [73-75]. With the advent of neurofeedback EEG became viable as a treatment option, being used for performance enhancement (academic, athletic or mental), and as treatment for ADHD, autism, Alzheimer's, post-traumatic disorders and substance abuse [76-80]. Thus since 1924 [81], the EEG has evolved from being an add-on tool in the diagnosis of brain health, to an instrument that is used for diagnosis, disease-staging [82-88], evaluation of prognosis including during the course of treatment (pharmacotherapy and chemotherapy) [89-93], and as itself as a therapeutic tool [76-80].

## EEG: Aiding diagnosis, preventing misdiagnosis and under-diagnosis

EEG has recently been used in the differential diagnosis of syndromes of uncertain etiology [94-97]. For example, subcortical ischemia or multiple infarcts or single strokes have been known to cause personality changes, affective disorders, and even psychosis. Similarly, psychiatric disorders such as obsessive compulsive disorder (OCD), schizophrenia, autism, dyslexia, and addictions have shown distinct differences in neurological features between subjects and controls. The EEG is also useful in distinguishing diseases with similar symptoms yet different etiopathophysiology. Cognitive impairments, for example, can be due to a range of reasons like electrolyte imbalance, hypoglycemia, sleep disorders, stress, head injury, pain, dementia, etc. [94].

Recently the EEG's potential to generate either early diagnostic markers or biomarkers has been explored for neurological disorders like AD [43-44], multiple sclerosis [47-49], Parkinson's disease [52-55], schizophrenia [98], autism [62-64], and dyslexia. A study on neurodegeneration and progression from mild cognitive impairment (MCI) to fully developed AD revealed significantly higher levels of delta bands among AD subjects, for example [84]. A 2-year longitudinal study on 86 MCI patients used six EEG biomarkers to successfully predict the conversion of 25 patients exhibiting beta activity to AD with 88% sensitivity and 82% specificity [86]. Automatic feature extraction techniques helped predict focal seizures increasing the sensitivity to 87.8% [88].

## Current EEG technology in a nutshell

The design, specification, maintenance and calibration protocols for electrodes [99-109], electrode placement systems [109-118], use of ground and reference electrodes, EEG machines (analog, digital or multi-channel), EEG calibrators and montages [119] are governed by stringent standards and guidelines [120-129]. EEG recording procedures are categorized into two stages: a) data acquisition and pre-processing, and b) feature extraction. The stages are performed as follows:

*Acquisition and pre-processing:* The EEG captures the pyramidal neuronal activity comprising action potentials (3ms) and postsynaptic potentials (200ms) via electrodes following an excitatory stimulus [98]. The 20μV signal is amplified using a differential amplifier, followed by normal amplifiers. High-pass (HPF), low-pass (LPF) and notch filters are then used to minimize/overcome/nullify "noise" arising from intrinsic and extrinsic factors, and the distortion caused by aliasing when the analog signal is digitized by the analog-to-digital converter [122-128].

*Artifact correction:* Correction for artifact removal or attenuation is carried out depending on the data and study design. Artifacts due to eye blinks or head shaking which are symptoms are attenuated and not removed. ICA (Independent Component Analysis) and SSP (Signal Space Projection) are some of the methods used for artifact attenuation [130-133]. Signal averaging, thresholding of the output, signal enhancement, and finally edge detection are then carried out.

*Data processing:* Processing of data includes feature extraction, selection and classification. In general for most digital EEG machines, feature extraction alone is carried out. Fast Fourier Transform (FFT), Wavelet Transform (WT), Time-Frequency Distributions (TFD), and Foreword and Inverse Source Space analysis are among the methods used for feature extraction [133-137]. Patient data is then stored for neuroclinical assessment and report generation [138-140].

## Software developments in EEG technology

Previously, the patterns of EEG wave forms/wave morphology alone were used in combination with other neurological tests to diagnose neurological disorders [141-143]. In more recent years the processed EEG data (wave forms) are quantified via quantitative EEG (q-EEG), wherein a specialized software program converts 1-dimensional (1-D) brain wave signals into 2-D topographical color maps comparing a patient's brain function to a normative database (Neuroguide, FDA research standard) [144-146]. The resulting color code allows for the generation of quantitatively relevant Z-scores. Another software development that revolutionized the field improving the spatial resolution of EEGs was the use of Independent Component Analysis (ICA) in combination with Low Resolution Electromagnetic Tomography (LORETA) [145-153] to transform 2-D into 3-D EEG data, which enabled locating the source of EEG waves on the cortical lobes. Source location (originally only possible via CT or MRI) is important as it enables identification of the functional regions involved in specific responses or disease states.

Figure 1 shows the components of the **NeuralScan** by Medeia a state-of the-art EEG computer-based system. It is in keeping with current standards and incorporates the most up-to-date technological improvements in the field of EEG machines. Figure 1A shows the 21-channel EEG cap. The built-in software can carry out routine clinical assessment of EEG wave forms (alpha, beta, theta or gamma) and wave forms tests, namely; resting-state EEG (eyes closed and opened). Or, the system can evaluate working memory and ERPs (Figure 1B) from evoked potentials (visual, auditory, odd ball paradigm) and behavioral motor tests. The system is capable of i) "automatic" artifact (blinks, pulse artifact, MR gradient artifact, ballisto-cardiogram, and bad blocks) removal via FFT, wavelet and ICA as well as ii) feature extraction, iii) frequency-based analysis of the EEG wave forms and iv) for transformation from the time domain to the frequency domain. The software can also perform qEEG for brain mapping, power and frequency analysis and comparison with a normative database provided with the package (Figure 1C) and with eLORETA to carry out source analysis (Figure 1D). Also provided with it is a neuropsychological questionnaire with some sections that the patient answers (self-reporting) and others that the clinician administers. The test takes in total 15 minutes to perform. The reporting system can be customized to make summarized reports that can be easily understood by physician and patient (Figure 1E), or detailed reports that can depict correspondence of EEG and vital signs (Figure 1F).

## EEG-based markers of cognition, mental and brain health

Normal EEG wave forms [154-156] vary with age, mental states and depending on if they are stimulus induced or resting-state. Abnormal wave form patterns [126,157] are subdivided into epileptic and generalized non-ictal wave forms and include: intermittent slowing, intermittent rhythmic delta activity (IRDA) continuous slow activity (diffuse slowing, alpha coma), periodic abnormalities (Burst suppression, periodic discharges (GPDs/SIRPIDS), and background suppression. Disease-specific patterns are also observed. For example, disease-specific EEG patterns have been noted in subacute sclerosing panencephalitis (SSPE) [158] and in Creutzfeldt-Jakob disease [159].

The processed EEG wave forms captured at a) resting-state EEG (eyes closed and opened), b) following a specific task (working memory) and c) event related potentials (ERPs) including evoked potentials (visual, auditory, odd ball paradigm) are the source of several brain health biomarkers [160-162]. Figure 1 summarizes wave types that can be used in EEG to provide information on neurological and mental health EEG-generated markers that have been used in both neurological/mental health research and for clinical assessment.

## Event related potentials (ERPs) in disease and research

Evoked or event-related potentials (ERPs) are obtained following an event/stimulus. The stimulus can be visual, auditory, motor or task related. Checker-boards with black and white squares with the black and white squares alternating their positions at a predefined period are often used as visual stimuli. They are presented on a computer screen for a specified duration, and as the brain is able to recognize the interchange in black and white squares within a fraction of a second; this recognition is captured in an EEG wave form. The epochs that capture one complete stimuli and response cycle are marked out and selected. As the stimulus/test duration may be 5 minutes. All the epochs pertinent to that duration and stimulus are similarly marked and selected. The averaged response to a particular stimulus provides the event-related potential (Figure 1D) for that stimulus. The ERP waveform has both positive and negative components which are denoted as "P" and "N"

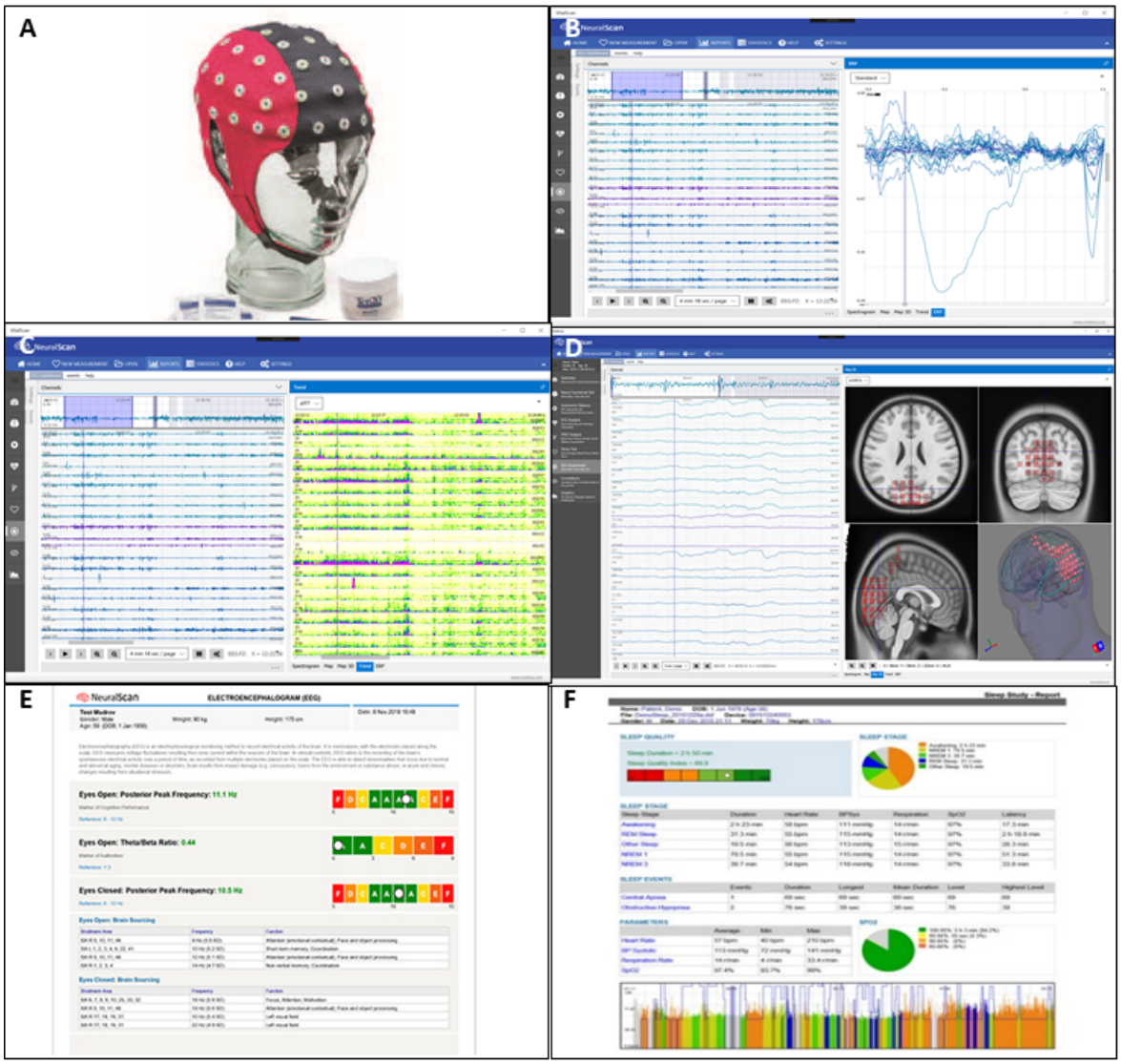


**Figure 1.** Components of Neuralscan by Medeia. (A) 21-Channel electroencephalograph (EEG) cap; (B) Signal averaging for event related potentials (ERP) generation; (C) Power analysis, frequency analysis, and QEEG mapping; (D) Source localization via exact low-resolution electromagnetic tomography (eLORETA); (E) simple report; (F) full report with time correspondence to vital signs reading

respectively with a number (P100 and N100) that either indicates the latency in milliseconds or the hierarchical position of the wave form.

In an ERP study of schizophrenic patients, P100 amplitude principal component analysis revealed that while the first principal component (global activity) and the second (reciprocal anterior-posterior activation) were similar in patients and controls, the third component (hemispheric reciprocity in activity) showed unique activation of the center versus anterior and posterior regions in patients with schizophrenia [163]. In a study on Autism Spectrum Disorder (ASD), autistic children exhibited longer P100 latencies, weaker N100 amplitudes and larger P300 amplitudes compared with typically developing (TD) children. [164]. ERPs detected in the early phase following traumatic brain injury have been found to serve as predictive markers for functional and cognitive recovery at six months post-injury [165]. ERPs have also been used to identify impairment in the dorsolateral prefrontal and anterior cingulate cortices in Parkinson's Disease [166]. EEG (non-linear complexity) in combination with a neuropsychological assessment (Alzheimer's Disease Assessment Scale-cognitive: ADAS-Cog) and cardiovascular history assessment was also found to increase diagnostic accuracy from 80% to 92% for distinguishing between AD, vascular dementia, mixed dementia, and MCI [82].

Specific cortical auditory evoked ERPs have also been used to identify sensitive period cutoffs for primary auditory cortical development in juvenile cochlear implant recipients [167]. Further, ERPs have been used to identify differential emotional processing based on responses to emotionally negative stimuli in veterans with PTSD [168]. A study of African American seniors has also found that EEG spectral power at rest with eyes closed during a One Card Back Learning test (OCL, memory) was able to differentiate those at-risk of MCI from those that were stable [32].

## Technological variants of EEG

In more recent years, specialized types of EEG have been developed for specific functions. Each of these provide unique advantages for applications in research or in the clinic. This section discusses two of the most common of these recent EEG-based technologies, quantitative EEG and low resolution electromagnetic tomography. (Table 1).

## Quantitative EEG (qEEG)

In Quantitative EEG (qEEG), EEG data is used to create 2-D topographical color-coded brain maps that reflect the Z-scores obtained of the patient's brain functioning when compared to a normative reference database (Neuroguide, FDA research standard) (Figure 1C). The waves are then analyzed to determine their distribution, power, ratio, coherence and connectivity across the cerebral lobes [144-146]. A study on the use of qEEG to monitor and aid in the treatment of traumatic brain injury (TBI) confirmed that alpha power (AUC=0.87, $p<0.01$) and variability of the relative fast theta power (AUC=0.84, $p<0.01$) demonstrated high prognostic value [17]. qEEG was also shown to have clinical diagnostic value for viral encephalitis, exhibiting a higher level of detail and precision compared with EEG [27]. Unusually high theta activity in the frontal region and higher theta-to-beta activity is observed in ADHD [169]. A review of studies on Parkinson's disease (PD) found slowing EEG frequencies to be correlated with a decline of cognition with increase of spectral powers in delta and theta and a decrease in alpha, beta, and gamma activity in this disease setting. Topographically the occipital, parietal, and temporal lobes also showed higher correlation with the spectral changes observed in Parkinson's disease [170].

## Low resolution electromagnetic tomography (LORETA)

In Low Resolution Electromagnetic Tomography (LORETA), [147-153] 2-D EEG data is converted into 3-D data to locate the

**Table 1.** EEG-based markers of brain/mental health

| | |
|---|---|
| **EEG** | • Wave form characteristics<br>• Peak frequency of the brain waves recorded<br>• Theta-Beta Power Ratio<br>• Clinical significance/relevance of a) Low peak frequency, b) High peak frequency |
| **Evoked Potentials & Event-related potentials (ERPs)** | • Visual evoked potentials (VEP), Auditory evoked potentials<br>• ERPs their mean and peak amplitude and latency across neuro- and mental disorders.<br>• Potential ERP based Brain Biomarkers: C1 and P1, P200, P300, P3a, P3b, P600, N100, N200, N2pc, N170, N400, Early left anterior negativity (ELAN). Error-related negativity (ERN), Late positive component (LPC), Lateralized readiness potential (LRP), Mismatch negativity, N2pc, Bereitschaft's potential, Contingent negative variation (CNV), Somatosensory evoked potential, Visual N1, ERP synchrony and ERP desynchrony.<br>• Odd ball paradigm, ERP: the P300 and the latency (in ms)<br>• Steady-state visual evoked potentials (SSVEPs), the brain responses to repetitive visual stimulation (RVS),<br>• Resting state EEG |
| **Frequency Analysis & qEEG** | • Absolute power (voltage, $P=mV^2$) in the patient's EEG database<br>• Relative power in a brain wave compared to the total power in a patient's EEG ($\theta/ \theta + \beta + \alpha + \Delta$)<br>• Inter- and intra-hemisphere coherence, right-left hemisphere and front-back balance in power and symmetry<br>• Ratios of the EEG brain waves (Hz) and their influence on brain and mental health?<br>• Mean frequency of the patient's brain waves.<br>• Z-score value of the patient's raw scores compared with the normative database – their direction and magnitude of the difference and their implications on brain health<br>• Appearance of the above variables if there is a local, focal, regional or generalized abnormality? |
| **sLORETA & eLORETA** | • Source of the electrical activity from the electrode/channel/derivation located in the brain<br>• Which Brodmann areas in the brain are involved?<br>• What are their cytoarchitecture, histology and function? |

source of the EEG waves on the cortical lobes. This in turn identifies the functional areas involved, localizing wave responses to the source to provide a neuroanatomical context (Figure 1D).

In a case study of ADHD investigating treatment with dopamine agonist KB200z, LORETA was used to successfully identify increased in frequency bands in the anterior, dorsal and posterior cingulate regions and right dorsolateral prefrontal cortex in response to treatment. Another study used LORETA to demonstrate increased dissociation between brain processes in schizophrenic patients, a key factor thought to account for the differences in the cognitive and emotional state of schizophrenic patients [98]. Specific LORETA parameters (current phase density and lagged phase synchronization) have also been successfully correlated with Aβ42 and total tau concentration in Alzheimer's disease patients. A LORETA z-score feedback approach has also been shown to reduce pain in head and neck cancer patients, improvements associated with modified brain activity in pain-associated brain regions. In another study comparing healthy individuals with patients with treated and untreated menopausal syndrome and depression, LORETA was used to successfully identify cortical anatomical correlates of depression as well as the pharmacotherapy mode of action. LORETA was also able to identify significant elevations in alpha activity in the precuneus, and posterior middle temporal gyrus and decreased alpha activity in the medial frontal cortex, including the anterior cingulate and the superior and medial frontal gyri, in migraine patients.

## Conclusion

The EEG has evolved in recent decades from a noninvasive monitoring tool into an instrument with diagnostic, prognostic and therapeutic/neurofeedback applications for neurological and mental disorders. Today's state-of-the-art EEG machines allow for spectral analysis using qEEG, and source analysis using LORETA. EEG-based technologies have also proven useful in the diagnosis of disorders with complex etiology and in the early diagnosis of cognitive impairment, providing clinicians with a valuable window of opportunity to implement preventive measures via lifestyle changes and/or therapeutic interventions. Today's state-of-the-art EEG machines, like NeuralScan by Medeia can perform tests with high accuracy within 15 minutes. Portability of current EEG machines allow for ease-of-use in public health and laboratory settings, as well as for research purposes and clinical use.

## Authorship and contributions

PM, CC, JL, MA, and SD all contributed equally to the writing, review, and approval of this manuscript.

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## Conflicts of interest

One author is employed by Medeia, Inc. that produces NeuralScan.

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