Chapter 3

Mathematical Foundations of Quantified Electroencephalography

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Abstract

The bioelectric function of the cerebral cortex is best characterized by an electroencephalogram (EEG). Numerous mathematical analytical tools have recently been developed to objectively study processes that are impossible to assess at a glance. The use of these tools is called quantified EEG (qEEG). We analyze some of the main tools used in numerical analysis. First, we describe the analog-to-digital conversion process and the Nyquist theorem. The fundamentals of spectral analysis in the frequency domain are then discussed, starting with the Fourier theorem. Given the limitations of this approach, two tools for analyzing time-frequency series, i.e., the power spectral density and wavelet transform, are introduced. Finally, we address some of the methods to assess the interaction between pairs of time series. The mathematical convolution process, the main tool to assess the combination of channels, and the auto(cross)-correlation are described. Although not based on this principle, the Pearson correlation coefficient is also shown to be a measure of correlation. Finally, after the Fourier transformation of the auto(cross)-correlation, a useful synchronization measure and coherence were obtained. We speculate that the discrepancy between the theoretical interest in these tools and their limited use in clinical practice can be partially explained by the limited knowledge and confidence in their use by clinical neurophysiologists. Therefore, the basics of these tools need to be elucidated such that they can be used by a growing percentage of neurophysiologists in their daily practice.
Keywords

Auto-spectrum; Coherence; Cross-spectrum; Fourier transform; qEEG; Periodogram; Wavelet transform

Introduction

The primary function of the cerebral cortex, i.e., the exchange of information by generating bioelectrical signals, is best characterized by electroencephalography (EEG). The ability of EEG to report changes in cortical physiology for long periods with optimum temporal resolution is largely due to the development of mathematical analysis tools for bioelectric signals, commonly known by the acronym qEEG (quantified EEG). qEEG is used to introduce elements of objectivity into the analysis of EEG records, making it less dependent on the subjectivity of the observer. qEEG provides access to physiological or pathological conditions that are impossible to evaluate with naked eye, such as the phenomena of correlation or spectral composition.

Recently, qEEG has also been successfully applied in intensive care units (ICU). Neurocritical patients often experience altered levels of consciousness, and clinical examination results are insufficient. The large volume of scientific work that has focused on EEG monitoring (m-EEG) in critically ill patients [1-4] has highlighted the high incidence of epileptic seizures and status, which, being non-convulsive, go unnoticed in a routine clinical exam. Accumulating evidence (summarized in a consensus document published recently by the American Society of Clinical Neurophysiology [5]) supports the use of m-EEG as a diagnostic tool to monitor and titrate therapy with antiepileptic drugs as well as for prognostic assessment. The utility of qEEG and its ability to display results that are easily analyzed by the clinician are clearly demonstrated in these studies.

However, qEEG is not only useful for critically ill patient but also to all other areas that require EEG. In fact, qEEG is being applied very intensively in the diagnosis of dementia [6-9], attention deficit hyperactivity disorder [10,11], psychiatric disorders (like schizophrenia, obsessive-compulsive disorder or depression) [12-17] and of course, epilepsy. However, the type of analysis used for epilepsy may slightly differ in the location of sources or spectral characteristics [18-20]. Moreover, qEEG is also used to study sleep [21].

In this review, we intend to provide a brief but useful summary of some of the most fundamental methods used in qEEG, especially those derived from spectral analysis, because the important clinical results that can be obtained through its use (and the possible misdiagnosis) depend on the correct application of mathematical basis of qEEG. The proper understanding of these methods is essential for the application of mathematical tools with confidence in clinical practice.
Analog-To-Digital Conversion

Digital signal processing necessarily involves the conversion of analog to digital signals. An analog signal is continuous over a time interval. Voltage signals can be represented as \( V(t) \), indicating that this signal is a function of time. These signals are converted into a series of numbers that can be stored, represented and mathematically analyzed.

Modern equipments in clinical neurophysiology (CNP) consist of cheap analog-to-digital converters (ADC) with high sampling rate multiplexers. Briefly, this process samples a registered potential value defined during a very short time interval (sampling period, or \( \Delta t \), usually measured in milliseconds or even microseconds \( s \times 10^{-3} \text{ to } 10^{-6} \text{ s} \)). Thus, the continuous signal is converted into a sequence of discrete measured voltage values at constant intervals of time (Figure 1). Therefore, the notation becomes \( V(n) \), \( n = 0, 1, 2... \) Therefore, a continuous function is mathematically changed to a discrete number series. The inverse of the sampling period is called sampling frequency, denoted \( \nu = 1/\Delta t \), and is measured in Hertz (Hz).

Importantly, the mathematical transformations of our records will consequently be a discretized, not continuous series, representing the mathematical peculiarities of the tools to be used and the possibility of errors introduced by the ADC itself.

**Figure 1:** Analog-to-digital conversion. Effect of different sampling rates on an analog signal (top) and the distortion of the morphology by decreasing the sampling rate. Time is measured in seconds. Each sampled point is represented by a small red dot, whereas the reconstruction of the signal (i.e., the straight line joining two consecutive points) is represented by a green line.
Although we will not discuss the Nyquist theorem in detail, we will briefly address it herein [22]. Specifically, the theorem states that to maintain all the original information of the analog signal (which is frequency or band-limited), the sampling rate must be at least twice the maximum frequency contained in the signal ($\nu_{\text{max}}$). Suppose we want to determine a signal whose smaller symmetrical element ($\Delta t_{\text{min}}$) has a duration of 1 ms ($10^{-3}$ s). Therefore, because $\Delta t_{\text{min}} = \nu_{\text{max}}$, the frequency will be $\nu_{\text{max}} = 10^3$ Hz. According to the theorem, $\nu \geq 2 \nu_{\text{max}}$, and consequently, $\nu \geq 2 \times 10^3$ Hz. This finding is more intuitively demonstrated in Figure 1. At least three time points are required to characterize the smallest element: one at the beginning ($t_{\text{init}}$), another at the maximum value ($t_1$) and another at the end ($t_{\text{end}}$), such that $t_{\text{init}} < t_1 < t_{\text{end}}$. If the difference between both ends is 1 ms, ($\Delta t_{\text{extrem}} = t_{\text{end}} - t_{\text{init}}$), the period between either end and the midpoint is one half; thus, $\Delta t_{\text{extrem}} / 2 = 10^{-3}/2$. Logically, to preserve these points, our ADC must be able to sample values at a frequency of $(10^{-3}/2)^{-1}$, which is 2 kHz, as shown above. This sampling rate is important because it clearly differs from the sampling frequency for scalp EEG, for which the highest frequency is 60 Hz (implying a Nyquist rate of 120 Hz) for an intracranial recording aimed to register fast ripples [23-25] to 500 Hz (which is a sampling rate of at least 1 kHz).

Signal Analysis in the Frequency Domain

Neurophysiological recordings in general and, in particular EEG, are always obtained as time-dependent functions, i.e., in the time domain. This somewhat cryptic expression refers to the mathematical formulation of a function for which the domain is the set of values that can take the function. In our case, the values are the instants of time between the origin of the record ($t_{\text{onset}}$) and the end ($t_{\text{end}}$), $t_{\text{onset}} \leq t \leq t_{\text{end}}$. Therefore, the domain is explicitly stated in parentheses as the dependent variable function, e.g., $V(t)$.

However, the time domain analysis does not allow us to access much neurophysiological information, such as the most important frequencies in the signal. Therefore, the analysis is moved to the frequency domain.

Before beginning, we will define a periodic function. This is any function that acquires the same value when a defined interval of time, called period ($T$, s), is reached, which is explicitly defined as $f(t) = f(t + nT)$; $n=1,2…$

The function value is equal at the following period $t + T$, $t + 2T$, $t + 3T$, etc. The trigonometric functions sine, cosine and their multiple combinations are typical examples of such functions.
Fourier’s theorem states that any periodic and continuous function $f(t)$ (of period $T$) that complies with specific mathematical conditions—that we will not describe here—can be written as an infinite sum of weighted sine and cosine functions (see [26] for a detailed description). This result is profound, especially because this approach can be used to describe functions that do not resemble the sine and cosine shapes (Figure 2). The Fourier’s theorem can be formally stated as follows:

$$f(t) = \frac{a_0}{2} + \sum_{n=1}^{\infty} a_n \cos\left(\frac{2\pi nt}{T}\right) + \sum_{n=1}^{\infty} b_n \sin\left(\frac{2\pi nt}{T}\right)$$

Equation 1

Generally, it is called angular frequency to $\omega = 2\pi \nu = 2\pi / T$, which is measured in radians/s (rad/s). We utilize the inverse relationship between $\nu$ and $T$ in this expression.

In this equation, two types of coefficients, $a_n$ and $b_n$, can be defined as follows ($a_0$ is $a_n$ when $n = 0$):

$$a_n = \frac{2}{T} \int_{-T/2}^{T/2} f(t) \cos\left(\frac{2\pi nt}{T}\right) dt; \quad a_0 = \frac{1}{T} \int_{-T/2}^{T/2} f(t) dt; \quad b_n = \frac{2}{T} \int_{-T/2}^{T/2} f(t) \sin\left(\frac{2\pi nt}{T}\right) dt$$

Equation 2

This general expression can represent different functions because the values of the coefficients will differ. Indeed, each function $f(t)$ will have a set of coefficients that

Figure 2: Fourier’s theorem. Reconstruction of the linear function $y = 3/5x$ defined between 0 and 5 by increasing the terms of the Fourier series (equation 1). A) $n = 1$ term, B) $n = 5$ terms, C) $n = 20$ terms. For each section, the graphs represent the following: a) Function to be set ($f(t)$), b) Representation of the coefficients as a frequency function (power spectrum); c) resulting function d) the obtained sum of the different spectral components.
are proper and determine its spectrum. To represent the
dependence of the function on each discrete frequency
(i.e., each \( n = 1, 2, \ldots \)), the coefficients of a frequency are
combined as the square of the absolute value of their sum,
i.e., for each \( n \), we calculate \( |a_n + b_n|^2 \) (figure 2).

However, Equation 1 is not very useful in practical
terms. To be usable, we must find a formula with man-
ageable results. To this end, we combined coefficients to
define a new coefficient, called \( c_n \).

\[
C_n = \frac{a_n - ib_n}{2} \quad \text{Equation 3}
\]

This expression introduces a new symbol, \( i \), which is
called the imaginary term and is defined as \( i = \sqrt{-1} \). This
number does not belong to the body of real numbers (\( \mathbb{R} \)) but instead is part of the complex number domain
(\( \mathbb{C} \)), designed precisely to determine the root of negative
numbers. Within the theory of complex numbers, the De
Moivre theorem [27] is extraordinarily important for our
purposes:

\[
e^{i\omega t} = \cos(\omega t) + i \sin(\omega t)
\]

Combining this theorem with the definitions of \( a_n \)
and \( b_n \) (Equation 2) and with Equation 3, the following
expression is obtained:

\[
c_n = \frac{1}{T} \int_{-T/2}^{T/2} f(t)e^{-i\omega t} dt
\]

Using this definition, equation 1 can be stated as fol-
lows (this proof is simple and omitted here):

\[
f(t) = \sum_{n=-\infty}^{\infty} c_n e^{i\omega t} \quad \text{Equation 4}
\]

The great advantage of this expression in equation 1
is that it is a symmetric series whose midpoint is zero. If
we change the period to infinity, i.e., \( T \to \infty \), and remove it
from denominator (a rigorous process that can be shown
to be valid), we can call \( F\{f(t)\} = c_n \) to obtain the continuous
Fourier transform (CFT).

\[
F\{f(t)\} = F(i\omega) = \int_{-\infty}^{\infty} f(t)e^{-i\omega t} dt \quad \text{Equation 5}
\]

The infinite series is then changed to an improper in-
tegral to obtain the following:

\[
f(t) = F^{-1}\{F(i\omega)\} = \frac{1}{2\pi} \int_{-\infty}^{\infty} F(i\omega)e^{i\omega t} d\omega \quad \text{Equation 6}
\]

which is the continuous inverse Fourier transform
(ICFT). Both equations 5 and 6 are a pair of Fourier trans-
forms. Consequently, applying operator F to the function \( f(t) \), which is defined in the time domain, will give its transform, \( F\{f(t)\} = F(i\omega) \), which is the equivalent function in the frequency domain. Note that \( F \), which represents an operator (i.e., a mathematical operation applied to a function or vector to obtain another), is not the same as \( F \), which is the transformed function. Furthermore, the inverse function, i.e., \( F^{-1} \), allows us to find the original function from the transformed one.

However, the transform of a function is a complex, not real function. Therefore, for \( x(t) \) series, the transform is \( F\{x(t)\} = X(\omega) \in \mathbb{C} \). Thus, to obtain a real function, we must multiply by its complex conjugate (see [28]) as follows:

\[
S_x = \frac{X^*(\omega)X(\omega)}{N} \quad \text{Equation 7}
\]

where \( N \) is the number of array elements used to calculate the transform. Consequently, the units obtained are the squared, i.e., to the power of two, units of the original function, called the power spectrum. The resulting function is a periodogram, \( S_x \). Therefore, we do not confuse the Fourier transformation of a time series with the periodogram. This form of analysis is useful to provide valuable information about the composition of the original signal frequency, which allows us to identify the dominant frequencies and better estimate the relationship between bands. Figure 3 shows an example of the use of frequency analysis. Figure 3A shows a periodogram obtained from an EEG (F3-C3) during an absence seizure in a patient with idiopathic generalized epilepsy and the same patient after the administration of midazolam (Figure 3B). The importance of these findings for the mathematical analysis of neurophysiological signals is difficult to overestimate [29-35]. Undoubtedly, this calculation can be considered the main tool for the numerical analysis of time series.

However, this type of analysis suffers from various problems, such as fluctuations caused by inconsistencies in the statistical estimation of the periodogram [21] or the fact that this analysis applies mainly to stationary signals (whose probability density distribution does not change over time [22]), which is not the case for most of the EEG signals. Therefore, to extend the power of spectral analysis signals to non-stationary or short-term signals, the analysis of time-frequency has been introduced, which consists of presenting functions that depend on both the frequency and time \( G(\omega, t) \).

Numerous techniques are available for time-frequency analysis (for a detailed description, see [21]), but a detailed analysis of these techniques is beyond the scope of this work. However, we will focus on two that are most commonly used: the power spectral density (PSD) and wavelet transform (WT).
Figure 3: Periodogram of EEG recordings. A) Left: Frontal differential register for an absence seizure (left). Right: periodogram with a spectral peak at 6.4 Hz indicating the main frequency of ictal activity. B) Registration (left) and periodogram (right) from the same patient following the administration of midazolam. Note that the theta peak has disappeared, whereas a maximum appears in the delta band. The overall structure of both periodograms is similar, although during the crisis, several beta peaks disappear with medication. Note that neither the gain of the records nor the periodograms is equal.

The PSD (see Figure 4A) represents the change in the frequency composition of a signal over time. It is estimated using spectral analysis methods, such as classical nonparametric methods (fast Fourier transform), model-based methods (autoregressive or moving average) or time-frequency methods, such as the short Fourier transform or wavelet transform [29,30,36-39]. In this type of graphic, one axis (horizontal in the example shown) represents the frequency, whereas the other (vertical) axis represents time. The recording is analyzed in fixed time windows (between 8 and 32 s, usually) from every periodogram. The spectral composition for each frequency and time is represented by a color code: red indicates the maximum power, and blue indicates the minimum power for the example shown (codes may vary in other cases). This analytical tool is useful, especially for neurophysiologists, allowing the identification of complex spectral changes over time at a single glance.

The other widely used tool is the wavelet analysis (WT). The general expression for a WT is as follows [40]:

\[ W(a,b) = \frac{1}{\sqrt{a}} \int_{-\infty}^{\infty} f(t) \psi^*(\frac{t-b}{a}) dt \]

Equation 8

where \( \Psi^* \) represents the type of wavelet used for the transformation and the asterisk indicates its complex conjugate (see [27]). In addition, two parameters are used to define the transformation, such as the scale factor, \( a \) (which is > 0), and \( b \), the positional parameter. The main property of this transformation is that it is linear and does not depend on the translation or magnification.

The form or type of wavelet varies [40], the most fre-
quent forms are the Haar, Daubechies, Morlet and Mexican hat forms.

To evaluate the properties of equation 8 in the frequency domain, the terms $W(a, b)$ and $f(t)$ must be transformed and used in equation 5. Subsequently, a convolution is performed (see below) with the signal for each wavelet scale (changing the value of $a$ in the equation 8). For subsequent scales, different values are color-coded according to their amplitude. Thus, by changing the scale, it can be repeatedly applied to the same wavelet signal to cover large frequency ranges.

Therefore, this transformation results in a more flexible representation of the time-frequency relationship, allowing the use of temporal analysis variable windows [21,41,42], such that large windows allow a finer frequency resolution, whereas smaller time windows are used to increase the resolution of high frequencies. This flexibility, which covers both the lower and higher frequencies, makes the WT an ideal tool for analyzing paroxysmal EEG patterns, such as ictal and interictal discharges. Therefore, a multi-resolution analysis method avoids fixed frequency classical Fourier analysis and similar methods [32] and allows the analysis of non-stationary signals, which in principle is prohibited in classical Fourier analysis.

The proper selection of the type of wavelet and the number of levels to be tested is very important for the decomposition of the signal. For a suitable choice, the dominant frequency of the signal must be considered.

**Figure 4:** A) Time-frequency analysis by PSD. Records (right) and the PSD (left) of two different channels obtained during a electrocorticography (ECoG) are shown. Two recordings for each channel obtained in different time windows are shown. The change in the dynamics of the system is well reflected in the spectral composition of the signal. See text for details. B) Time-frequency analysis by WT. The spectral composition is shown for a wide frequency range (y axis) of a typical spike-like element.
Measures of Interaction Between Two Signals

Before addressing the interaction between signal pairs, we must briefly introduce a mathematical operation called convolution. It is a method to combine two signals, one of which is shifted in time by a defined amount. For signals $x(t)$ and $y(t)$, the convolution ($\otimes$) is defined as follows:

$$x(t) \otimes y(t) = \int_0^t x(\tau)y(t-\tau)d\tau$$

In essence, a signal ($x$) is multiplied by the offset from the other version (i.e., $y(t-\tau)$), and this produces a unique value that is the area (i.e., the defined integral) under the resulting function of the product.

However, the convolution calculation is often complex, and it is consequently transformed into frequency domain to facilitate calculation. Using equation 5, the transform of the convolution of two time series can be shown to be the product of their transforms ($X(\omega)$ and $Y(\omega)$) (this proof is simple and omitted here [22]):

$$F\{x(t) \otimes y(t)\} = X(\omega)Y(\omega)$$

We can now analyze the measures that will determine the relationship between two time series. The correlation determines the dependence between two samples. This measurement can be performed on a single series, a process known as autocorrelation, or between two different time series, which is called cross-correlation. In both cases, the convolution is essentially calculated as shown above [22]:

$$C_{xy}(\tau) = \int_{-\infty}^{\infty} x(t)y(t+\tau)dt \quad \text{Equation 9}$$

Equation 9 is the expression for the cross-correlation, whereas the expression for autocorrelation is $C_{xx}(\tau)$.

These measures not only identify and quantify a relationship between two time signals but also indicate the time point of maximum (or minimum) delay. This method provides information on the directionality of the interaction and the time required for the transmission of that relationship. Another useful tool for assessing the relationship between two time series is Pearson’s correlation [43], which is defined as follows:

$$\rho = \frac{\int_{-\infty}^{\infty}(x-\mu_x)(y-\mu_y)dxdy}{\sigma_x\sigma_y} \quad \text{Equation 10}$$

where $\mu_x$ and $\mu_y$ are the mean values of both series, and $\sigma_x$ and $\sigma_y$ are the standard deviations.

This measure indicates the degree of linear dependence between the two series. However, it does not provide
exactly the same information as the correlation measurements based on convolution. In fact, it is not possible to correlate to the same signal (which would be \(\rho_{xx}\)) because the value will always be a maximum (\(\rho = 1\)) in this case. Furthermore, considering the entire signal, a time value, \(\tau\), is lacking. Therefore, the spread of information between the two series cannot be determined.

Figure 5 shows an example of the information provided by these tools for two time series that are related to differing degrees, varying from two equal sine series (5A) to two completely random series (Figure 5C).

The Fourier transform of equation 9 provides an interesting aspect that links correlation measures to the spectral component of a signal pair. In fact, the following is easily demonstrated for this transformation [22]:

\[
F\{C_{xy}\} = X^*(\omega)Y(\omega)
\]

In other words, the Fourier transform of the cross-correlation results in the cross-spectrum \(S_{xy}\), which is the product of the Fourier transform of both functions, wherein the asterisk indicates the complex conjugate. In the case of autocorrelation, transformation gives the power spectrum or periodogram. This fact is very important because it demonstrates that the power spectrum of a time series represents the same information as its auto-correlation.

Finally, we will analyze the ultimate tool of analysis, which is obtained directly from the above and is called coherence (C). It is defined as follows [22]:

\[
C(\omega) = \frac{|S_{xy}(\omega)|^2}{S_{xx}(\omega)S_{yy}(\omega)}
\]

Therefore, coherence is the ratio of the square modulus of the cross-spectrum for two time series x and y divided (or rather, normalized) by auto-spectra (or periodograms, namely \(S_{xx}\) and \(S_{yy}\)). This measure is advantageous because it allows us to determine the synchronization between the signals for a particular frequency band (therefore, its dependence on the angular frequency is explicitly stated), instead of calculating the degree of synchronization for the entire band, such as for the Pearson correlation. This is very important because the coherence for a particular band of the EEG spectrum is often high, but this high coherence is not observed in the other bands. Figure 6 shows a real example of the use of coherence during a seizure. We can observe an increase in the coherence for theta band during the post-ictal state compared with the pre-ictal state. This fact allowed us to identify a real ictal state (discarding non-epileptic psychogenic seizure). The patient was then studied using deep electrodes in order to ultimately provide an intervention.
Figure 5: Relationship between time series. A) Equal sine series (absence of random noise), $\rho = 1$. B) Mixing signals of the sine function more random noise, $\rho = 0.328$. C) Two signals consist of purely random noise $\rho = 0.012$. The third row of each section displays the presentation cross-correlation function (in A would be in reality autocorrelation). Note that the correlation is maximized in the same time intervals in A and B, although its size is smaller in B. However, C shows no evident correlation.

Figure 6: Utility of coherence in clinical practice. A) Recording of a generalized crisis (blue bar) with anomalous behavior that may appear to be a non-epileptic psychogenic seizure. The record is full of artifacts by muscle activity. B) Analysis by bands of pre-ictal of time (red bar) and post-ictal (yellow bar) periods. The black line in each graph indicates the average value of coherence, whereas
the green dashed lines show the levels of $\pm 2.5$ standard deviation. The horizontal red line shows the level of significance. The red arrow indicates the increase in coherence approximately 5 Hz after the episode, an effect that was not present before the episode (in fact, the remaining bands are not affected). C) Average coherence for each scalp electrode (shown as proportional to the diameter of each electrode) and for each frequency band before and after the episode. In the theta band corresponding to the graphic, the average coherence in the electrodes of the right temporo-parietal region is increased.

**Conclusion**

The various tools for time series analysis in general and for neurophysiological EEG recordings in particular have experienced extraordinary development during the last quarter century. Not only have the field applications of these tools increased, but also several new techniques that promise to further expand this range, such as techniques that address the functional connectivity of EEG [44-48] or synchronization measures [49-51], have also been described.

However, a significant gap exists between the theoretical and scientific development of the field and its clinical application. In fact, these tools (other than spectral measurements and correlation) are not routinely used in clinical practice, despite the considerable increase in publications describing their use. We attribute this lack of use to several reasons: i) the lack of interest of commercial firms in the generation of easily programmable and accessible applications to implement these tools; ii) the mathematical complexity of some of these tools, which sometimes requires MATLAB®, R or other languages and hinders their implementation by clinicians; and iii) mainly, the general lack of confidence of neurophysiologists when using these tools. The latter is likely the strongest limitation to the clinical use of qEEG. For a neurophysiologist faced a diagnostic problem, knowledge and confidence in what he/she is doing is essential, given the clinical, ethical and legal implications of his act. Therefore, a trusted method of analysis, such as conventional EEG analysis, is preferable to ensure solid and informed knowledge of treatment and diagnosis.

However, scientific articles demonstrate the diagnostic and prognostic utility of qEEG [5,9,11,16,17], which encourages its implementation. Therefore, we believe a deeper understanding of these mathematical tools for an increasingly large group of neurophysiologists is essential to begin using quantified analyses for clinical practice. Thus, we will soon achieve a quantitative change in the diagnostic and prognostic value of EEG, a greater inter-observer coincidence and an undeniable increase in the scientific basis of the theory of EEG, which is the main knowledge gap in this scientific field [52]. Ultimately, these measures will increase our understanding of the brain.
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