TITLE: **Clinical applications of EEG power spectra aperiodic component analysis: a mini-review**

Authors: Sara Maria Pani [a], Luca Saba [a], Matteo Fraschini [b]
[a]Department of Radiology, AOU di Cagliari, s.s. 554 Monserrato (Cagliari), Italy
[b]Department of Electrical and Electronic Engineering (DIEE), University of Cagliari, Piazza d'armi, Edificio M, Cagliari, Italy

Corresponding Author: Sara Maria Pani
Department of Science of the Images, Policlinico Universitario, University of Cagliari, asse didattico E, ss 554 bivio Sestu 09042, Monserrato (Cagliari), Italy.
Email: s.pani4@studenti.unica.it

Declarations of interest: none

Highlights

- A comprehensive quantification of EEG (electroencephalographic) signals avoids misinterpretation of band-limited power differences
- Aperiodic component features are proposed as possible biomarkers of a variety of medical conditions
- Raising awareness might boost related research and challenge traditional approaches to diseases diagnosis, treatment and follow-up.

Abstract

Objective

The present mini-review summarizes recent clinical findings related to the analysis of the aperiodic component of EEG (electroencephalographic) power spectra, making them quickly accessible to our target audience of medical specialists and allied health researchers, with the final aim of boosting related research.

Methods

Based on our own experience about clinicians' literature-searching habits, we queried the PubMed database with specific terms related to EEG power spectra aperiodic component analysis and selected clinical studies conducted on patients that referenced such terms in the title/abstract, and were published in the last five years.

Results

A total of 11 journal articles, dealing with 9 different neurologic and psychiatric conditions and published between 1st January 2016 – April 1st 2021, were surveyed.

Conclusions

Despite the heterogeneity of diseases and aspects investigated in the selected papers, the shared key points relate to the exploration of i) the pathophysiological significance of the aperiodic component of the EEG power spectra, ii) its impact on the traditional approach to oscillatory features, iii) its correlation with the presence/absence of pathology and with diseases stages and/or severity.

Significance

All studies reported relevant results about aperiodic activity significance, with findings that might possibly challenge the traditional approach to the diagnosis/treatment/follow up of the pathology considered.

Keywords

Electroencephalography; power spectrum; aperiodic component; neural noise; 1/f; clinical EEG studies.

1. Introduction

The human electroencephalogram (EEG) recorded from the scalp has a frequency spectrum that is a mix of narrow-band oscillations (e.g., alpha and beta activity) and a non-oscillatory activity or broadband noise, which is dominant in lower frequencies (Barry and De Blasio, 2021). Non-oscillatory brain activity is also termed 'aperiodic' or 'arrhythmic', namely without a predominant temporal frequency, and 'scale-free' in reference to its scale-invariant nature (He et al., 2010).
Between the oscillatory activity, also called 'periodic' due to the particular temporal frequency of the patterns, and the aperiodic activity, we find quasiperiodic oscillations with intermediate characteristics, which exhibit recurrent patterns with an irregular period (Palva and Palva, 2018). While oscillations with stable periods retain their peaks both in single trials and in averaged power spectra, aperiodic signals lack of peaks both in single trials and in averaged data; quasiperiodic oscillations, with their high variable periods, may exhibit peaks in single trials that might not be retained in averaged power spectra data, making them indistinguishable from the spectra of aperiodic signals (Palva and Palva, 2018). Through the years, a considerable proportion of EEG literature focused on differences in pre-defined frequency bands, with a prolific production of studies evaluating the oscillatory neural activity in both typical and clinical groups. A less rigorous approach has been reserved to the aperiodic activity, and the colors neural noise could assume are still not fully explored by research (Doyle and Evans, 2018). Naming colors of noise is common in other fields (Doyle and Evans, 2018) as audio engineering, electronics and physics, with *color of noise* referring to the power spectrum of a noise signal. Noise colors relate to the probability distribution of the amplitude and the power of noise across the frequency spectrum. Colors mostly assume Gaussian amplitude distribution and differ only in their power spectral density (Doyle and Evans, 2018).
A generic term used in literature to refer to any noise with a power spectral density $S(f)$ described by equation (1) is 1/f noise.

$$S(f)\ \alpha\ \frac{1}{f^{\alpha}} \qquad (1)$$

In this equation (1) f stands for frequency and the values α may assume determine the color of noise. α also determines the power of noise changes across the frequency spectrum (Ward and Greenwood, 2007). The canonical case with α = 1 is called pink noise, and it is ubiquitous both in nature and man-made processes (Bak et al., 1987).
Pink (1/f) noise refers to a general form of noise which is intermediate between the white noise (α =0), with its equal intensity at different frequencies, and brown noise (α =2) or Brownian motion, which describes a random walk (Ward and Greenwood, 2007). 1/f noise exhibits typical attributes of healthy complex systems, namely a combination of dynamical minimal stability (the system is barely stable with respect to small perturbations) and adaptability (Bak et al., 1987; Stadnitski, 2012). In virtue of its fractal structure, it has characteristics that remain similar when viewed at different scales of time or space (self-similarity), and this same structure gives it two essential properties: i) a very slow decaying autocorrelation function (ACF), namely a long-memory of the process (vs the theoretical one of i) white ideal noise – no memory, ii) brown ideal noise -infinite memory); ii) a power-law distribution, in which the power of noise is inversely proportional to the

frequency (Stadnitski, 2012). The latter becomes evident plotting the power spectrum on a log-log scale, with the logarithmic power function of 1/f noise that follows a straight line with slope equal to -1.

Bak et al. (Bak et al., 1987) were the first to link together fractal geometry, 1/f noise and power-laws, introducing the concept of self-organized criticality (SOC) and laying the foundation for modern 1/f research. SOC phenomenon is observed in particular complex systems with extended degrees of freedom, which operate near the critical configuration (minimal stability), with no need of fine-tuning by an external factor (Bak et al., 1987; Ward and Greenwood, 2007). The neural criticality hypothesis is controversial (Hesse and Gross, 2014) and although self-organized criticality and fractal temporal dynamics have been often used to explain 1/f brain activity (He, 2014), an unequivocal link between the phenomena is still missing and other models were proposed to account for 1/f activity (Bédard et al., 2006a; Miller et al., 2009; Muthukumaraswamy and Liley, 2018), leaving the question open about what types of neuronal processes are responsible for these potentials. Specifically, as summarized by Muthukumaraswamy and Liley (2018), the existence of power laws in the brain has been argued to depend on the state of self-organized criticality of the brain, poised on a boundary between two qualitatively different dynamical states and identified as the best state for information transmission (Beggs, 2008), or might be potentially explained by low-pass filtering of ionic current flow at dendritic processes (Lindén et al., 2010; Robinson et al., 2001), as well as might be created by current flow in the extracellular space, consisting in a complex folding of intermixed layers of fluids and membranes (Bédard et al., 2006b), if the media is considered as a complex arrangement of resistors and capacitors (Bédard et al., 2006a).

A significant fraction of the spontaneous electrical field potentials of the EEG (electroencephalographic) recordings is represented by the aperiodic 1/f component of the power spectrum that constitutes the arrhythmic and scale free brain activity (He et al., 2010) and may be characterized in terms of slope, also referred as spectral exponent, namely the exponential decrease of power in a spectrogram as a function of frequency, and offset of the broadband power of the signal (He, 2014) (See Fig. 1 for a graphical display of aperiodic component's features). It is of great importance to note that while the study of pure 1/f noise is, by definition, free from frequency ranges, the physiological 1/f-like noise is not. EEG recordings are in fact an intricate combination of non-stationary oscillatory rhythms overlapping the 1/f spectrum (Muthukumaraswamy and Liley, 2018), which makes the accurate estimation of the aperiodic features, and of the slope in particular, not straightforward. The implication is that, even disregarding oscillations, the aperiodic component is not purely a line in the log-log plot, but it shows bends or "knee" frequencies, where the 1/f spectrum deviates from linearity. The estimates of the slope of 1/f like noise generally lie in the range between $0 < \alpha < 4$, and typically between 1 and 2. While we can state pink noise and brown noise have an exponent of 1 and 2 respectively, it is important to consider that these exponents are not exclusive to noises and might be generated by different processes, biological ones for example. A knee point has been found at ∼20 Hz by Robinson et al (2001) whose model reproduced the sleep-related steepening of the 1/f-like decay in the low frequencies, attributing it, as well as the knee at higher frequencies, to the aforementioned low-pass filtering properties of the dendrites. Consistently, Colombo et al. (2019) found a steeper decay in the higher-frequencies during wakefulness and xenon/propofol anesthesia, with the knee once again at ∼20 Hz; to obtain a better

local fit they splitted the broad 1-40 Hz band examined in two sub-bands (1-20 Hz; 20-40 Hz) that interestingly revealed a different response to pharmacological manipulations, suggesting independent neuronal timescales are at a play. A simulated network including both excitatory and inhibitory populations modeled by Gao et al. (2017) suggested a crucial role of blocking activity propagation in steepening the PSD (power spectral density) decay. Excitatory and inhibitory inputs have different rates of decay, and changes in the relative contribution between their synaptic currents seem to be reflected in the field potential, namely in the frequency domain representation (PSD) (Gao et al., 2017). Gao et al. (2017) demonstrated how changes in the spectral exponent might depend on global changes in the excitation/inhibition (E/I) balance (e.g., an increased contribution of the inhibitory population, with reduction of the E/I ratio, steepens the decay) and how, vice versa, E/I changes can be estimated from the power law exponent. This general concept, confirmed by physiological, computational and pharmacological evidence (Colombo et al., 2019; Gao et al., 2017), offers an important starting point for the study of those clinical conditions in which the E/I tone has a relevant role.

While the aperiodic signals of neural field recordings have been linked to the underlying activity of postsynaptic potentials (Gao et al., 2017; Miller et al., 2009), neural oscillations are thought to relate to population synchrony (Donoghue et al., 2021) and to possibly facilitate the dynamic temporal and spatial organization of neural activity (Voytek and Knight, 2015). Neuronal activation has been shown to result in a flatter slope (He, 2011), reflecting decreases in lower-frequency power and increases in higher-frequency power (Podvalny et al., 2015), suggesting that slope flattening and spectral power associated changes might be a signature of increased asynchronus neuronal activity (Peterson et al., 2017; Sheehan et al., 2018; Voytek and Knight, 2015).

Consistently, Muthukumaraswamy and Liley (2018) demonstrated temporal correlations between oscillatory alpha power and the estimates of the slope (in high frequency bands: 5-100Hz) in EEG, ECoG (Electrocorticography) and MEG (magnetoencephalography). Considering the EEG spectra as being generated by a collection of stochastically perturbed damped oscillators with a distribution of relaxation rates, they proposed a model that possibly explains the nature of 1/f signal, its sensitivity to drug interventions, as well as its dynamic interaction with oscillatory rhythms (Muthukumaraswamy and Liley, 2018). Nevertheless, this dynamic interaction between the periodic and aperiodic component of EEG power spectrum is still under investigation.

The aperiodic activity is the prevailing one when the oscillatory component is absent (Schaworonkow and Voytek, 2021), however most of the EEG studies are conducted on an ex ante basis taking in consideration canonical frequency bands to be investigated and ignoring the aperiodic “background activity”, often simplistically defined as noise. On the contrary, as has been stressed by recent works (Donoghue et al., 2020b), the aperiodic signal may instead correspond to physiologically relevant signals, with their peculiar functional significance.

In contrast with the traditional view, several experimental findings confirm not only a significance behind part of the signals usually considered as noise, but also the dynamism of the aperiodic component, expressed by the changes in its parameters in relation to task demands (He et al., 2010), cognitive states (Podvalny et al., 2015), age (Schaworonkow and Voytek, 2021; Tran et al., 2020) and also diseases (Peterson et al., 2017; Robertson et al., 2019). Furthermore, already in 2001 Robinson et al. (Robinson et al., 2001) provided a theoretical basis for the conventional division of

EEG spectrum into frequency bands, highlighting, at the same time, how the exact bounds are not universal but dependent on the individual. The common thread of individuality has been explored in the following years with studies that showed the important role that the subject-specific characteristics of EEG features may play for clinical purposes (Arns, 2012; Demuru et al., 2017; Fraschini et al., 2015; Pani et al., 2020; Rocca et al., 2014) In this context, it has been recently demonstrated by Demuru and Fraschini (2020) that the aperiodic component also is characterized by strong subject-specific properties and that its features may help to characterize and make inferences at the single subject level, with a better performance than that of the classical frequency bands.

Not surprisingly, the traditional approach derives from partially arbitrary choices of the principles to be considered fundamental for the study of EEG signals and it would be definitely interesting to know what the differences in the EEG analysis routine would be if in the past the 1 / f exponential distribution had been defined as a core characteristic of EEG signals (Donoghue, 2020).

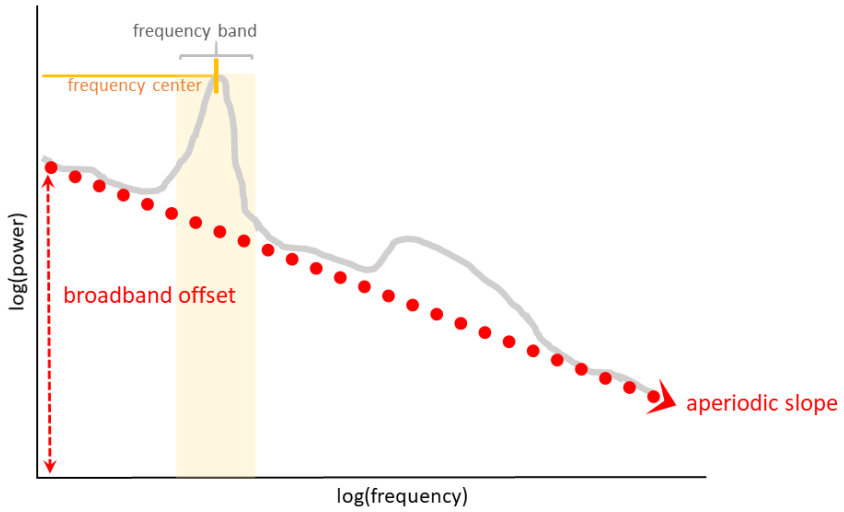
The focus on the oscillatory component of EEG power spectra was strengthened by the selective attention scientists paid to it over the years, at the detriment of the aperiodic component, albeit unconsciously. In fact, although the first study dealing with the exponential distribution (1/f-like) of EEG data dates back to 1949 (Donoghue, 2020; Motokawa, 1949), it was followed by years of silence before being revived by Freeman, who worked on the topic through all his career and summarized the main concepts in a four part work: “Origin, structure, and role of background EEG activity” (Freeman, 2006, 2005, 2004a, 2004b), and then Pritchard (1992) and He et al. (2010). Voytek's group is, in recent years, the most prolific on the subject, with several studies (e.g., Peterson et al., 2017; Robertson et al., 2019; Voytek et al., 2015) aiming at characterizing the EEG aperiodic component in different groups and investigating its physiological and clinical significance.

In light of these findings, and considering that the oscillatory component is embedded in the non-oscillatory one (Donoghue et al., 2020b), it would be appropriate to take the non-oscillatory activity into account to avoid misinterpretation of band-limited power differences. In fact, being the aperiodic component omnipresent, non-zero power is always detectable at all frequencies bands, meaning that any spectral measure (e.g., computing a power spectrum, narrowband filtering, and average band-power measures) will return a numerical value of power for any chosen frequency band even when there is no oscillatory activity at all (Donoghue et al., 2021). Donoghue et al. (2021) recently proposed a very valuable 7-point checklist of methodological considerations and recommendations for a correct analysis and interpretation of neural oscillations. They provided a comprehensive overview of neural oscillations heterogeneity and addressed, among the other topics, the periodic/aperiodic issue. Donoghue et al. (2021), once again, highlighted the importance to evaluate to which of the elements of the data (periodic/aperiodic) the changes detected should be attributed, and have drawn attention to methods that can be used i) to separate and measure aperiodic neural activity as IRASA (Wen and Liu, 2016), and ii) to measure and control for aperiodic activity such as spectral parameterization (Donoghue et al., 2020b) and eBOSC (Kosciessa et al., 2020).

In summary, approaching EEG data with an a priori classical analysis focused on the periodic component of EEG power spectra, fails to answer the question: are the changes detected driven by

the oscillatory component alone? The power changes may indeed result from i) the periodic signal, ii) the aperiodic signal, iii) a combination of the two components, periodic and aperiodic.
In spite of it, while the oscillatory component has been extensively investigated far less, attention was and is reserved to the changes of the aperiodic component, while conducting clinical EEG studies.
With the final aim to boost the research related to the field, we realized this mini-review, revising recent clinical studies that included the aperiodic component analysis in their methods, defining field of interest, nature of the results and possible clinical impact. The 5-year criterion for our selection is based on the technical progress of the last five years regarding methods/tools to measure the aperiodic component features. Modern approaches enable a precise and uniform evaluation of aperiodic features and, consequently, the chance to produce, with little effort, reproducible and comparable results. Hoping to raise interest in our target audience made of medical specialists and allied health researchers, we focused on clinical outcomes of PubMed searches, ensuring an easy retrieve of the articles discussed for eventual further information. As a matter of fact, PubMed is one of the most widely accessible biomedical resources globally (Williamson and Minter, 2019) and also, in our experience, the most used database by clinicians colleagues.
Our PubMed search of indexed articles on the topic resulted in two macro-areas of application, namely psychiatry and neurology. All of the studies, despite the heterogeneity of the topics, showed relevant results concerning aperiodic activity significance and highlighted the utility of the comprehensive approach to EEG power spectra features in avoiding misinterpretation of band-limited power differences, and in exploring the role of the aperiodic features as possible electrophysiological biomarkers.

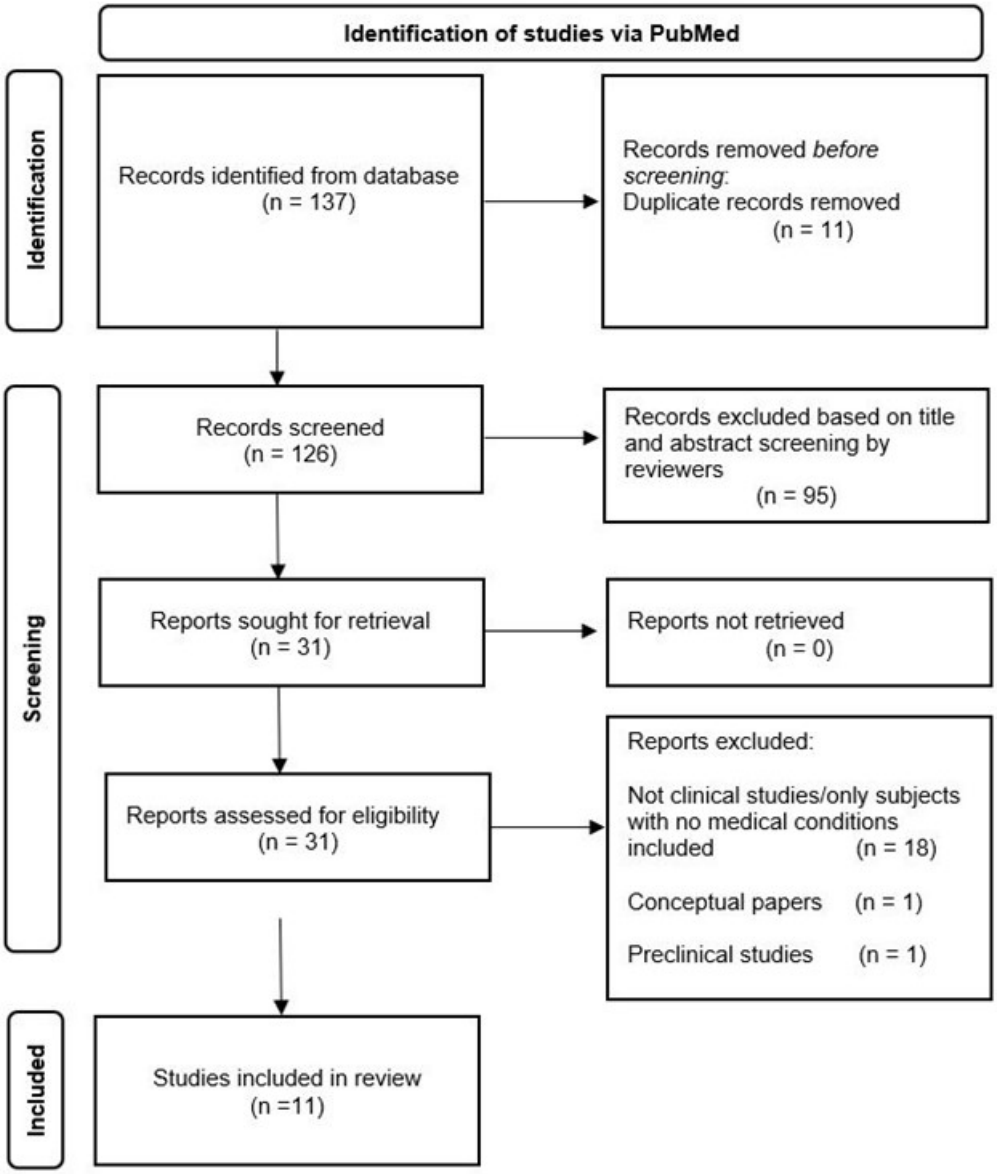
Fig. 1 Periodic and aperiodic spectral features. Example of an EEG signal (grey): marked in yellow a peak in one of the canonical frequency bands (yellow stripe); in red the broadband offset and the slope that characterize the aperiodic component of the power spectra.



2. Methods

In order to achieve our goal, searches were performed on the PubMed database to select articles from the last five years that referenced the following items/terms in their title or abstract: 1) aperiodic component of power spectrum; 2) EEG power spectral slope OR EEG power spectral offset; 3) Aperiodic EEG activity; 4) 1/f brain activity OR 1/f neural noise. Eligibility criteria included i) type of study: clinical studies conducted on patients/patients and controls, ii) date of publication: last five years (1st January 2016 –1st April 2021); no language and length restriction were imposed; no unpublished studies and/or not indexed articles were included due to the choice to query only PubMed. A total of 11 studies were identified for inclusion in the review. The search of PubMed provided a total of 137 citations, and after adjusting for duplicates, 126 remained. Of these, 95 were excluded, after reviewing the titles and abstracts, due to clearly not meeting the criteria. Full text of 31 reports that appeared to meet the inclusion criteria, or on which there was uncertainty, were accessed, and 11 studies were selected after excluding the ones not relevant to the current project (studies on subjects with no medical conditions/preclinical studies/conceptual papers). We detailed reports selection using PRISMA 2020 flow diagram (Page et al., 2021), see Fig. 2. Details about selected studies and main results concerning patients' aperiodic activity features are shown in table 1. The authors of the selected papers used a variety of terms to define changes of the exponent of the aperiodic component. To facilitate the reading and comprehension of the results we limited the heterogeneity using "steeper" each time the authors described an increase in the absolute value of the slope and "flatter" each time they described a decrease in the absolute value of the slope.

Fig 2. PRISMA 2020 flow diagram showing studies selection.



Tab. 1. List of studies selected.

Study	Year of publication	N° of subjects	Condition	Main Results Aperiodic activity - PATIENTS	Method/Tool	Frequency range considered to estimate 1/f activity*
Robertson et al.	2019	126 [76 patients – 50 controls]	ADHD	Drug naïve: greater offset and steeper slope.	FOOOF	4-50 Hz
Pertermann et al.	2019	61 [29 patients – 32 controls]	ADHD	Engaged in response inhibition processes: flatter slope in theta band.	MATLAB (script not available)	0.5 -20 Hz
Levin et al.	2020	51[25patients-26 controls]	ASD	Agreement across recording sessions: fair for the offset; good for the slope.	FOOOF	1-100 Hz
Molina et al.	2020	67 [36 patients - 31 controls]	Schizophrenia	Steeper slope + normalization of the slope with 20 mg of memantine.	FOOOF	4-50 Hz
Veerakumar et al.	2019	4 patients	Depression	Right hemisphere slope changes (steeper slope during treatment response) track sick/well states during ongoing SCC-DBS.	Not reported	2–48 Hz
Roche et al.	2019	94 [57 patients – 37 controls]	Rett Syndrome	Steeper slope + slope association with lower cognitive scores.	MATLAB (code not available)	2-24 Hz
Martin et al.	2018	13 patients	Parkinson Disease	1/f broadband activity confounds the relationship between beta activity and motor symptoms.	MATLAB (script available at request)	8-90 Hz
Belova et al.	2020	22 patients	Parkinson Disease	Slope difference during rest and voluntary movements (flatter slope during movements) correlates with motor signs severity. Slope sensibility to short-term changes.	Neurodsp	1-300 Hz
Semenova et al.	2020	9 patients	Cervical Dystonia	Asymmetric difference of the slope in the internal segment of globus pallidus: flatter in the ipsilateral to the head-turning.	FOOOF	30- 70 Hz
	2021			Flatter slope contributes significantly		

Wilkinson & Nelson		35 [11 patients – 24 controls]	X Fragile Syndrome	to the increase in high-frequency power. Aperiodic component driven increase of gamma power was associated with better language ability.	FOOOF	2-55 Hz
Pani et al.	2021	31 patients [15 SHE- 16 NREM p]	NREM sleep disorders	Steeper slope in NREM parasomnia patients than in SHE patients, sleep stage N3.	FOOOF	0.5 -50 Hz

ADHD: attention deficit hyperactivity disorder; ASD: autism spectrum disorder; SCC-DBS: subcallosal cingulate cortex - deep brain stimulation; NREM: non-rapid eye movements; NREM p: non-rapid eye movements parasomnia; SHE: sleep-related hypermotor epilepsy. * The frequency ranges reported have been deducted by the authors, they were in fact not uniformly reported in the reviewed papers.

3. Results

In this section we summarized salient clinical findings concerning the aperiodic activity; the selected studies are divided by macro-area.

3.1 Psychiatry

3.1.1 Attention deficit hyperactivity disorder (ADHD)

ADHD is a neurodevelopmental disorder, which can persist into adulthood, characterized by hyperactivity or impulsivity and inattentiveness (American Psychiatric Association, 2013). ADHD has been represented as an evolving construct shaped over the last decades by research into its clinical nature and structure, and it keeps changing depending on new findings (Posner et al., 2020). ADHD diagnosis is still clinical and requires a detailed and complex evaluation not only of current/previous symptoms and functional impairment but also of the full family, gestational, and developmental history (Barkley, 2002). It is therefore understandable how a lot of efforts have been made toward the identification of a biomarker of ADHD diagnosis and symptomatology. A large body of research has focused on resting state electroencephalography (EEG), searching for differences in the EEG power spectrum, with Lubar in 1991 (Lubar, 1991) who was the first to suggest the use of increased ratio of theta to beta power (TBR) as a measure to distinguish children affected by ADHD from typically developing ones. However, the elevated theta/beta ratio seems to be more reliable as prognostic than diagnostic measure, as demonstrated by Arns et al. (2013) in their meta-analysis conducted on the TBR in ADHD children/adolescents, and its relationship with behavior remains uncertain (Zhang et al., 2017). Current approaches calculate theta/beta ratio using fixed frequency bands, without considering the other relevant features of the power spectrum as possible confounders.

In this framework fits the study by Robertson et al. (2019) in which they quantify not only features derived from the oscillatory component but also the spectral slope and offset from the aperiodic component of EEG power spectra, in the resting-state EEG of 3- to 7-yr-old children affected by ADHD and controls. Robertson et al. demonstrated that i) medication-naïve children with ADHD had higher alpha power, greater offsets and steeper slope when compared with typically developing children and ADHD children in treatment (despite a 24-h medication-washout period); ii) the spectral slope positively correlated with the traditional theta/beta ratio, even if they did not find a significant group difference in the ratio in their sample. Putting together this findings and past research we may conclude, as suggested by the authors, that band-limited theta/beta ratio calculations may inconsistently capture the shift in low-relative to high-frequency EEG power in ADHD, and that the slope may have an important role as neural marker, more than traditional approaches, taking also in account its association with executive functioning and excitatory/inhibitory balance. The results highlighted the possible role of the spectral slope in reflecting pathology in the brains of ADHD children, as well as the effects of stimulant medication.

Pertermann et al. (2019) focused instead on task-related EEG and neural noise following research trends about a low stability of neural processes in ADHD. Assuming that the lack of stability may relate to increased level of neural noise, they examined 1/f neural noise of EEG data collected during

a response inhibition (Go/NoGo) task, and the effects of methylphenidate treatment on children affected by ADHD. The data showed higher neural noise in ADHD children than in healthy controls when engaged in response inhibition processes in the theta band only, namely a flatter slope of the 1/f neural noise, that is generally considered crucial for cognitive control (Cohen, 2014). The authors then hypothesized that neural noise is not elevated on a general basis in ADHD, but with regard to highly demanding inhibitory control processes. Furthermore, they suggested that the effectiveness of the first-line pharmacological treatment with methylphenidate in treating cognitive dysfunction and impulsivity, depends on the action it has in reducing the neural noise to the level found in healthy subjects.

3.1.2 Autism spectrum disorder (ASD)

ASD is a set of neurodevelopment disorders resulting from complex genetic and environmental risk factors interactions, and characterized by deficit in social behaviors and non-verbal interactions, with an impairment of communication, and restricted, repetitive, or stereotyped behaviors (Barbaresi et al., 2006; Park et al., 2016). Although several variables impact treatment outcomes (Ben Itzchak and Zachor, 2011), early intervention programs seem to be beneficial for children with ASD, improving developmental functioning and decreasing maladaptive behaviors and symptoms severity (Rogers and Vismara, 2008). In the absence of definitive diagnostic tests, clinical evaluation following DSM-V criteria (American Psychiatric Association, 2013) remains the gold standard for diagnosis, and biomarker development is a high priority in neurodevelopmental disorder research. EEG is a promising tool for the development of biomarkers in neurodevelopmental disorders, and the resting state EEG PSD in particular is considered a potential biomarker in the field of autism spectrum disorders based on reported differences in resting state EEG PSD among patients and typically development children (Wang et al., 2013). In this context Levin et al (2020) estimated test-retest reliability, in a short time span (~6 days), of the profile of the EEG PSD in children with ASD and typical development. To characterize the profile of the PSD they used two approaches i) FOOOF (fitting oscillations & one over f) algorithm (Donoghue et al., 2020b), with the estimation of six parameters (offset, slope, number of peaks, and amplitude, center frequency and bandwidth of the largest alpha peak) that characterize the shape of the EEG PSD; ii) non-parametric functional data analysis, with decomposition of EEG PSD shape into a reduced set of principal component functions that characterize individual power spectrum shapes. Non-parametric functional data analysis and FOOOF approaches were proven to be complementary in characterizing the PSD, and the alpha peak derived from FOOOF-based parameterization, in particular, has the highest test-retest reliability both at intra-subject (amplitude) and inter-subject level (center frequency). The offset was fairly stable in both groups across sessions; the slope showed a good agreement in the ASD group but was unstable in the control group across sessions, and possible explanation were sensitiveness to session effects, older mean age and/or lower mean IQ of the ASD group, very little inter-individual variability in the control group. Levin et al (Levin et al., 2020) demonstrated the utility of resting EEG PSD shape and some of its specific parameters as stable biomarkers of cortical activity over short time windows, suggesting their potential role as biomarkers of traits or diagnosis. Despite a wide focus not restricted to the aperiodic component, this work by Levin et al (2020) highlighted some of the

benefits of their use of a comprehensive approach to EEG power spectrum: fitting and interpretation of FOOOF parameters was more direct than in the non-parametric approach, and the parameters seemed to be less susceptible to artifact contamination than non-parametric analysis. Not to be neglected, FOOOF measuring of putative oscillations does not need predefining specific bands of interest and controlling for the aperiodic component.

3.1.3 Schizophrenia

Complexity and heterogeneity are crucial characteristics of schizophrenia and make it a severe psychiatric disorder with important behavioral and cognitive repercussions. Lot of efforts have been made to understand the origin of this complex syndrome and it seems to lie in genetic and/or environmental disruption of brain development (Owen et al., 2016). In lack of diagnostic tests or biomarkers the diagnosis is clinical, based on history and mental state (American Psychiatric Association, 2013). The disorder generally arises with psychotic symptoms that seem to be linked to dysfunction of dopaminergic neurotransmission, although the dysfunction appears to be more spread than originally thought and to involve different areas and circuits (Sakurai et al., 2015; Uhlhaas and Singer, 2015). The severity of this disorder has a deep impact on patients' quality of life, and a multidisciplinary approach is a must to effective management; antipsychotic medication needs to be combined with psychological therapies, social support and rehabilitation (Lenroot et al., 2003).

Molina et al. (2020) focused on an interesting aspect of the disorder, namely the biology underlying cognitive symptoms that are pervasive and refractory to conventional treatment. Based on the proposed role of the aperiodic component in indexing tonic E/I balance (Gao et al., 2017), Molina et al. (2020) applied FOOOF algorithm (Donoghue et al., 2020b) to EEG recordings acquired during EAIP (early auditory information processing) testing, evaluating a sample of patients and healthy controls with the aim to investigate said balance and its abnormalities in schizophrenia patients, assessing its changes in response to memantine.

The results confirmed the presence of deficits in the E/I balance of treated schizophrenia patients, described by a steeper periodic slope, and that E/I balance can be transiently normalized with a single 20-mg dose of memantine. Interestingly, the slope feature extracted from the aperiodic component of the EEG signal seems to be a candidate for the role of biomarker of cortical E/I balance.

3.1.4 Depression

Depression is a mental disorder with a complex nature and course that has a high worldwide incidence and prevalence. It has generally an early age onset, high chronicity, and function impairment that diminishes quality of life (American Psychiatric Association, 2013). The presentation may be heterogeneous and its detection, diagnosis, and management is challenging for clinicians, taking into account not only the unpredictable course and prognosis, but also the variable response to treatment (Malhi and Mann, 2018). A large portion of patients recover, often not permanently, but there is also a part of them that is treatment-resistant (Al-Harbi, 2012). One of the experimental therapies for treatment-resistant depression is deep brain stimulation (DBS);

Veerakumar et al. (2019) focused on subcallosal cingulate cortex (SCC) DBS in their observational study of four patients receiving therapeutic DBS while concurrent bilateral local field potential recording. Among the potential sources of the aperiodic component of EEG power spectrum, the activity-dependent dendritic filtering (Pettersen et al., 2014) and the E/I balance of brain networks (Voytek and Knight, 2015) are the ones that involve its responsiveness to neural inputs, suggesting its sensitiveness to experimental manipulation. By exploiting this putative propriety, Veerakumar et al. (2019) studied the sources of variance of SCC-local field potential slope magnitude in pre-treatment recordings, and explored the possibility to use 1/f slope to track modifications of depression severity scores by studying both parameters changes during the six months of deep brain stimulation that the four patients underwent. Bearing in mind cohort size (n=4), the results seem to suggest the potential utility of the 1/f slope as putative biometric of longitudinal DBS-facilitated antidepressant effects, right-hemisphere slope changes indeed appear to discriminate sick/well states during ongoing SCC-DBS treatment in three of four subjects, namely right hemisphere slope steepened in the setting of treatment response.

3.2 Neurology

3.2.1 Rett Syndrome

Rett syndrome is a devastating neurological disorder that impacts brain development and function and affects almost exclusively females. In most of the patients diagnosed with classic Rett syndrome the recognized causes are the loss-of-function mutations in the X-linked MECP2 gene, encoding methyl-CpG-binding protein 2 (Ip et al., 2018). The normal early development is followed by a subsequent regression, with the symptoms beginning around 12-18 months and progressing to cognitive, motor, sensory and autonomic dysfunction (Neul et al., 2010). Common features are motor dysfunction, loss of acquired verbal skills, intellectual disability, replacement of normal hand function with stereotyped repetitive movements and epilepsy (Ip et al., 2018; Neul et al., 2010). The need of objective biomarkers to assess brain function and disease severity in patients affected by Rett syndrome is explained by their objective difficulties in verbal communication and intentional hand use, which make the clinical evaluation challenging.
In this context Roche et al. (2019) examined EEG spectral power and 1/f slope of girls affected by Rett syndrome and typically developing girls, to determine if there were group differences and dissimilarities within the patients group in relation to various clinical characteristics. The results showed lower power in middle frequency bands, higher power in lower frequencies and a significantly steeper slope in girls affected by Rett syndrome, with the last two in association with lower cognitive scores. The increased power in lower frequency bands accords with previous studies that proposed a “slowing” of the background activity in Rett syndrome (Niedermeyer et al., 1986), and the increase in delta band specifically is suggested to be linked to an abnormal cortical inhibition due to dysfunctional GABAergic signaling; the significant differences in the 1/f slope seen in patients might reflect an abnormal excitatory/inhibitory balance within the brain. Delta power increases in association with the altered spectral slope are then supposed to accurately reflect the alterations

of neural circuitry in Rett syndrome and are proposed as potential markers of severity according to their link with more severe phenotypes and the worsening with disease progression.

3.2.2 Parkinson Disease

Parkinson disease affects more than 6 million individuals worldwide and is the most common in a group of neurological disorders called parkinsonism (Armstrong and Okun, 2020). It is a heterogeneous syndrome that could have a rapid or slow progression, and is characterized by motor symptoms such as rigidity, bradykinesia, tremor, postural instability, and disability in functional performance (Miller, 2002). The disorder may also, in addition to the characteristic motor features, be associated with non-motor disturbances (Davie, 2008). The heterogeneity also reflects in the etiopathogenesis, with extensive regions of the nervous system involved, several neurotransmitters and protein aggregates implicated, leaving the root cause of the syndrome unknown; the disease seems indeed to result from genetic and environmental factors that affect numerous fundamental cellular processes (Kalia and Lang, 2015). Parkinson's typical movement disorders result from dopamine deficiency within the basal ganglia, due to the early prominent death of dopaminergic neurons in the pars compacta of the substantia nigra (Kouli et al., 2018). The diagnosis of PD (Parkinson disease) remains essentially clinical, and involves evaluation of both symptoms and history, as well as the exclusion of other causes of parkinsonism (Bloem et al., 2021; Marsili et al., 2018). Nowadays we just have symptomatic therapies, namely dopamine-based treatments that enhance intracerebral dopamine concentrations for motor symptoms, or selective serotonin reuptake inhibitors for psychiatric symptoms and cholinesterase inhibitors for cognition, but we do not dispose of disease-modifying drugs (Armstrong and Okun, 2020).

Extensive studies demonstrated that abnormally synchronized activity of the basal ganglia-cortical loop correlates with motor impairments in both humans and animal models with Parkinson's disease, and the suppression of excessive synchronization is the target of dopaminergic, ablative and deep-brain stimulation therapies (Hammond et al., 2007). The excessive synchronization of beta oscillatory activity in local field potentials (LFP) recorded from the subthalamic nucleus (STN) has been linked with bradykinesia and rigidity severity, and proposed as potential biomarker of disease state, however the functional role of beta activity in untreated Parkinsonian state is still not clear, with a marked inconsistency between different studies (e.g., Ray et al., 2008; Chen et al., 2010).

Martin et al. (2018) hypothesized that the influence of the electrophysiological broadband activity may confound measurements of beta activity in STN recordings and it may have led to the inconsistency between previous studies. Using both modeled and actual data of thirteen patients affected by Parkinson disease they showed that beta oscillatory activity is significantly correlated with bradykinesia and rigidity only when 1/f broadband activity is not considered in the biomarker estimation. The electrophysiological features were evaluated taking 6 minutes of resting state STN LFPs bilaterally and motor clinical scores were evaluated immediately afterwards. They basically isolated beta activity from the potential confounder represented by the broadband activity, evaluating the impact the latter has on the relationship between beta activity and motor symptoms. No correlation was found between broadband activity and PD motor symptoms. The principal implication of Martin et al. (2018) results concerns closed-loop deep brain stimulation, where the

stimulation is triggered only according to the occurrence of the proposed biomarker: pathological beta activity (Iturrate et al., 2018). Furthermore, the importance of data-driven models is highlighted, as well as the need for a careful identification of biomarkers for symptom severity and close-loop applications.

Belova et al. (2021) approached the association between synchronization and clinical signs comparing LFP signals in the STN of parkinsonian patients at rest and during voluntary hand movements occasionally followed by leg movements, by use of two methods: raw power approach and 1/f -corrected approach. For subsequent legs movements but not for hand movements they found a significant increase in the low beta range, with each of the two approaches. Both movements were instead associated with a significant increase in gamma range synchronization using the raw power spectra approach, and a significant decrease in the slope (flatter slope) of the aperiodic component using the 1/f corrected approach. Belova et al. (2021) results support the theory of 1/f slope as possible indicator of excitatory/inhibitory projections ratio in the recording site, and also suggest the slope as a useful measure on the basis of is sensitiveness not only to static or long-term changes in brain states but also to transient specific states. The study by Belova et al. (2021) was indeed the first one in which the 1/f aperiodic slope was evaluated in its short-term changes (for time periods <20 sec) with the aim to detect LFP features' dynamical changes in voluntary movement. To be noted that Belova et al. (2021) found a significant correlation between the difference in the slopes during rest and movements, and the severity of PD motor signs.

3.2.3 Cervical Dystonia (CD)

Dystonia is a hyperkinetic movement disorder that is characterized by sustained or intermittent muscle contractions that cause abnormal and often repetitive movements and/or postures (Batla, 2018). Voluntary action seems to initiate or worsen dystonia and it has an association with overflow muscle activation (Albanese et al., 2019). The most common type of focal dystonia is the cervical one that causes an abnormal and asymmetric head position manifested by neck rotation or tilt (Fahn et al., 1998). Several different theories were proposed about the origin of CD, the more recent seem to unify the previous, proposing a head neural integrator connecting cerebellum, basal ganglia and proprioceptive network in a circuit that form the final common pathway for head position control (Popa et al., 2018; Sedov et al., 2019b). The asymmetric contraction of muscles in CD is thought to be linked to lateralized differences in pallidal outflow (Moll et al., 2014). Although the estimation of spectral power in specified frequency bands is the traditional method used for interhemispheric asymmetry studies, Semenova et al. (2020) decided to include in their analysis the aperiodic component of the EEG power spectra, measuring bilateral pallidal LFP of nine CD patients during DBS surgery, to examine the effects of the lateralized asymmetry on the 1/f broadband activity. In 2017 Gao et al. (2017) proposed the role of 1/f signal in reflecting the balance of the E/I inputs, while in 2015 Voytek and Knight (2015) proposed the impact of the same signal on neural communication. Relying on these two assumptions, Semenova et al. (2020) hypothesized that a lateralized increase of the broadband activity may be a possible signature of impaired asymmetric feedback to the neuronal integrator. The results highlighted a trend towards an asymmetric difference in the 1/f broadband activity in all patients, namely the ipsilateral 1/f slope of the

broadband activity in the internal segment of globus pallidus was flatter than the one of the other side, confirming previous findings about a higher inhibition of the pallidum contralateral to the head-turning (Sedov et al., 2019a). They also found asymmetry in oscillation scores of low-beta and alpha frequency bands for globus pallidus internus and globus pallidus externus respectively. Semenova et al. (2020) point out the importance of integrating periodic and aperiodic analysis to a complete approach to the study of the pallidal asymmetry in CD patients.

3.2.4 Fragile X Syndrome (FXS)

FXS is a trinucleotide disorder in which a repetition of the CGG motif on the X chromosome leads to silencing of the Fmr1 gene and to a consequent reduced expression of its product, namely Fragile X Mental Retardation Protein (FMRP). The FMRP has a key role in gene expression and regulation of the translation of a high number of mRNAs, many of which are implicated in mechanisms for development and maintenance of neuronal connections (Hagerman et al., 2017). The disorder is the most common inherited form of intellectual disability and autism spectrum disorders; children affected by FXS often present, in addition to cognitive deficits, language impairments, seizures and severe behavioral alterations such as hyperactivity, impulsivity and anxiety (Hagerman et al., 2009). Although the progress made towards the understanding of neural mechanisms that underlie FXS deficits and, consequently, the identification of targets for therapeutic intervention, the lack of clinical biomarkers contributes to limit the process of translation of therapeutics form laboratories to clinical practice. EEG alterations showed by both adult humans and Fmr1 KO mice (Ethridge et al., 2019; Wang et al., 2017) could be considered as potential biomarkers, nevertheless, as observed by Wilkinson & Nelson (2020), the absence of studies on young children complicates the identification of developmental timing of the EEG changes. Wilkinson & Nelson (2020) conducted the first EEG study focused on preschool/young school aged boys affected by full-mutation FXS, to investigate the presence of baseline EEG abnormalities analogous to FXS adults' ones, and the relationship between baseline EEG measures and several cognitive measures. Periodic and aperiodic components of EEG power spectra were compared using non-parametric cluster-based permutation testing. It was demonstrated that resting-state measures from young boys with FXS identified alterations in gamma power similar to the ones reported in adults and mouse models. Participants affected by FXS presented increased power in the beta/gamma range (~ 25-50 Hz) across several regions (e.g., Frontal cluster, FXS vs age-matched controls, vs cognitive-match controls) and, although the aperiodic slope showed just a marginally significant trend in reduction (flatter slope) for patients vs age matched controls (frontal and central regions), it contributed significantly to the increase in high-frequency power, and drove the gamma power increase that was found to be associated with better language ability in the FXS group. The latter association between resting state aperiodic gamma power and language development is in contrast with previous findings, and Wilkinson & Nelson (2020) hypothesized that some EEG alterations may be able to reflect ongoing homeostatic compensatory mechanisms in young children, based on the concept of an increase in gamma activity in response to altered cortical spiking resulting in an E/I imbalance, but normalized firing rates. No associations were found between gamma power and parent report measures of behavioral challenges, sensory hypersensitivities, or adaptive behaviors.

3.2.5 Non-Rem Sleep Disorders

The differential diagnosis between non-rem (NREM) parasomnias and sleep-related hypermotor epilepsy (SHE) is one of the most difficult challenges for sleep physicians and epileptologists. NREM parasomnias are defined as abnormal behaviors arising typically from sleep stage N3, and are common during both childhood and adulthood (Greenblatt, 1992). These sleep disorders encompass confusional arousals, sleepwalking, night terrors, as well as lesser-known entities as sleep-related violence/eating disorder and sexsomnia (Hrozanova et al., 2018), and in case of particularly violent clinical occurrence might be mistaken for sleep-related hypermotor epilepsy seizures. SHE seizures, on the other hand, may arise in unconventional ways such as wandering, complex automatisms or vocalizations, and in this case may be easily mistaken for parasomnias (Derry et al., 2006). The clinical overlap of the two sleep-disorders, and the lack of specific electrophysiological biomarkers, confirmed nocturnal video-polysomnography as the gold standard for differential diagnosis. Being the latter an expensive, time consuming and operator-dependent procedure in which the video component is essential to formulate the diagnosis, a lot of efforts have been made to find objective parameters to make the diagnostic process easier and quicker.

As with most clinical studies, sleep analysis focuses generally on the oscillatory activity and its distinct frequency bands. However, there are some exception; Lendner et al. (2020) for example, proposed the spectral slope as a marker of arousal levels in humans, with a clear role in facilitating reliable discrimination of wakefulness from propofol anesthesia, NREM and REM sleep. Shifting from the traditional to the comprehensive approach to EEG power spectra, our research group carried out a study (Pani et al., 2021) that included the extraction and examination of the slope and the offset, hypothesizing a disease-specific (SHE; NREM parasomnias) physiological significance of the features of the aperiodic component. For features extraction, we selected segments of multichannel sleep EEGs free from clinical episodes, deriving from the first part of the night and from N2 - N3 stages only, of two groups of patients affected respectively by NREM parasomnias and SHE. We found a difference in the gamma frequency band, with an increased relative power in SHE subjects in both N2 and N3, and a significant steeper 1/f slope in NREM parasomnia patients during N3. The results of this preliminary study suggested that the relative power of the gamma band and the slope extracted from the EEG signal may be helpful, in combination or disjointed, to support the differential diagnosis between NREM parasomnia and SHE in subjects with uncertain clinical features. Further investigations are however needed to confirm their potential role as possible electrophysiological biomarkers.

4. Limitations

In this work we did not discuss individually the limitations reported by each of the reviewed articles based on the heterogeneity of the topics covered and, consequently, of the specific nature of the limitations. However, some of the main points shared in turn by different studies concern i) the use of a new signal processing method and the inherent natural risks in results rendering, ii) the need of replications in larger samples size to assess the generalizability of the results and, on the other hand, the difficulty of patients recruitment for rare conditions and the consequent variability in terms of age, disease stage and severity, iii) the need for further investigations to clarify the precise contribution of excitatory and inhibitory signaling to the aperiodic slope for diseases in which the E/I tone has a relevant role.

We must point out that information about the studied frequency range is often not mentioned and/or difficult to find in the papers we considered. It is relevant to notice that differences in the frequency ranges examined might affect comparisons between results from different studies, and that the field would greatly benefit from a systematization of this information that would, in first place, promote reproducibility.

It is also very important to highlight that the aperiodic components of the power spectra may be influenced, and thus affected by several sources of noise, namely electrooculographic (EOG) activity steepens the slope and electromyographic (EMG) activity flattens (Schaworonkow and Voytek, 2021). As a consequence, we would like to stress the importance of limiting as much as possible these confounders before estimating and interpreting the results of the analysis. Another issue we would like to highlight, which may be particularly relevant for clinicians, is the inherent connection between EEG slowing (a typical effect of brain injury) and 1/f slope. In this context, it is interesting to notice how the spectral exponent may be used as index for the longitudinal assessment of stroke recovery (Lanzone et al., 2021). Moreover, we want to stress that other quantitative EEG metrics (i.e., EEG mean/median frequency, spectral edge, spectral entropy) have been used in this research field to estimate EEG slowing and that have been shown to be affected by power spectrum rotation (which clearly induces changes in the slope of the spectrum).

Although modern research on the aperiodic component introduced new interesting opportunities of development of diagnostic and therapeutic strategies for psychiatric and neurological conditions, the number of studies regarding clinical area is still relatively small, and this reflects in a lack of uniformity in terms of sample tested and tools/methods used even when a specific disease is considered. The lack of a generally accepted method to measure the aperiodic activity, in particular, makes the attempts of integration of the results tricky and undermines the reproducibility.
Similar challenges are faced by groups dealing with cutting-edge research topics, an example could be modern network science. As early as 2014, Stam (2014) warned the researchers in the field against the pitfalls in comparing results from different studies and different technologies, and about the need to minimize arbitrary choices in the analysis process to guarantee reproducibility as well as a uniform interpretation of the outcomes. Even from the same data, if analyzed with different methods, we can come to slightly different conclusions (for an explicative example see the results

from the functional connectivity studies conducted by Sabaroedin et al. (2019) and Pani et al. (2021) on the same data).

Finally, a specific limitation of our mini-review is the arbitrary choice to only focus on outcomes from PubMed database searches. Although we are aware that including other search services (e.g., Google Scholar or bioRxiv) would have brought to a higher number of articles, the choice is in line with the defined research topic. PubMed is in fact not only one of the most widely accessible biomedical resources globally but also, in our experience, the most used database by clinicians colleagues. Following the idea of a target audience made of medical specialists and allied health researchers, we excluded from this mini-review preclinical and non-clinical studies.

5. Conclusions

In this review of studies, a total of 11 journal articles published between 1st January 2016 – April 1st 2021 were surveyed, each of them comprising the extraction and examination of the features of the aperiodic component of EEG power spectra. In these papers, despite the heterogeneity of the diseases or aspects investigated, the shared key points relate to i) the exploration of the eventual pathophysiological significance of the aperiodic component of the EEG power spectra as described by Donoghue et al. (2020a, 2020b), ii) the evaluation of its impact on the traditional approach to oscillatory features (Samaha and Cohen, 2021), iii) the estimation of its correlation with the presence/absence of pathology and with diseases stages and/or severity.
All studies had relevant results concerning aperiodic "background" activity significance, with findings that might possibly challenge the traditional approach to the diagnosis/treatment/follow up of the pathology considered.

We can certainly deduce, from the majority of the evaluated studies, that there is no doubting about the potential clinical utility of a comprehensive quantification of EEG power spectra features. A clear advantage of including the analysis of the aperiodic component in the pipeline of EEG clinical studies, with an explicit parametrization of neural power spectra, is the appropriate physiological interpretation of the results, with a more precise definition of which components of the data change and in which way. Seems in fact to be confirmed that the a priori classical approach, focusing on the periodic component alone, is no longer sufficient; it lacks in fact of measurement specificity failing to ensure the dependence of the changes detected from the periodic component alone (Donoghue et al., 2021).
The mystery of "neural noise" has been systematically ignored because of the difficulty linked to its interpretation and, at present, we still do not have a conventional widely accepted view of the physiological basis of this signal. However, on the base that it may correspond to physiological relevant signals with functional significance (Donoghue et al., 2020b; He et al., 2010), it is clear the need to take it into account for two principal purposes, as proposed by most of the studies considered in this analysis: avoid misinterpretation of band-limited power differences and, in light of its partial independence from the oscillatory component, explore its possible role as electrophysiological biomarker.

As mentioned previously, the physiological underpinnings of the aperiodic component have been evaluated by different research groups, and some studies suggested that the spectral slope reflects neural signal-to-noise ratio (Voytek et al., 2015) and that it is an index of the E/I balance in the cortical circuitry (Gao et al., 2017). These general concepts are common starting points of several of the studies reviewed, namely the ones treating clinical conditions in which the E/I tone has a relevant role. It should be borne in mind that it is tricky to cluster different pathologies (and relative pathophysiologies) on the sole basis of an electrophysiological characteristic (e.g. the steepness of the slope), especially when: i) this comparison is not meant from the beginning with an appropriate study design; ii) the number of subjects involved in the studies is still exiguous; iii) the numbers of clinical papers based on this specific EEG feature is limited; iv) the pool of pathologies is broad and

heterogeneous. Nevertheless, we tried to explore any commonalities in the considerations drawn by the authors about their results.

The slope is thought to reflect abnormal E/I balance in the brain circuits and a steeper slope has generally been seen as a reflection of an enhanced signal-to-noise ratio and thus increased GABA signaling and/or reduced glutamate signaling (Gao et al., 2017; Voytek et al., 2015). Consistent with the idea of the slope as index of E/I balance, Pertermann et al (2019) demonstrated a reduction of neural noise in patients with ADHD through methylphenidate; its action of inhibition of the reuptake of dopamine and norepinephrine results in the normalization of E/I balance and reflects in the normalization of the slope. In patients with ADHD, we might expect a flatter slope linked to a reduction in GABA signaling and/or increases in glutamate signaling, with a predominance of excitation on inhibition. Robertson et al (2019), which on the contrary found a steeper slope in a group of children with ADHD, conjectured the existence of a range of cognitively optimal spectral slopes for each developmental stages, with slopes "too flat" or "too steep" leading to cognitive impairments; they also hypothesized that the patients, tested in circumstances that asked for high cognitive control, might have developed some sort of compensatory mechanism which implies an increase in GABAergic activity.

A similar mechanism might interest patients with schizophrenia, which is generally associated with reduced GABAergic inhibition in the cortex (Lewis et al., 2005). We might expect, as for ADHD, a flatter slope in patients compared with controls, however Molina et al (2020) detected steeper slopes in patients during a passive auditory oddball paradigm. They also demonstrated a normalizing effect of memantine on patients' slopes, providing evidence of the utility of indices of E/I balance as metrics of pharmacologic sensitivity in drug discovery. Again, these findings seem to reflect a compensatory increase in GABAergic activity of patients with schizophrenia during passive auditory information processing.

Another group which, as schizophrenia patients, presents a more negative slope (steeper slope) compared with controls is represented by girls with Rett Syndrome (2019). The girls affected by Rett Syndrome showed also a significant variability in the slope, which Roche et al (2019) suggested to potentially represent both abnormalities in excitatory and inhibitory connections, and significant individual differences in neural connectivity and E/I balance.

In accordance with the state of hyperexcitability observed in rodent models of Fragile X syndrome, Wilkinson&Nelson (2021) found a flatter slope in patients affected than in controls. A possible explanation for the inhibitory dysfunction in FXS patients and the consequent increase in E/I ratio, might represent, again, a compensation mechanism for altered cortical spiking in order to normalize firing rates. Wilkinson and Nelson hypothesized that the above-mentioned increase in E/I ratio might be in the end functionally beneficial to FXS patients, as supported by their results of better language ability linked to aperiodic driven increase of gamma power.

Following the previous reasoning, in healthy subjects the shift from motionless state to motor activity leads to a decrease in the E/I (excitation > inhibition) ratio due to a reduction in total power of the indirect pathway in the network of basal ganglia, resulting in a steeper slope; this is in accordance with Belova et al (2021) results, which reported an anomalous flatter slope in the subthalamic nucleus during movements in patients with Parkinson's disease, as well as a correlation

of the decrease with motor signs severity. They also confirmed the utility of the slope to determine short term dynamical changes in local field potential features during voluntary movement.
E/I balance is also recognized as a preclinical measure of interest in the pathophysiology of anhedonia which is one of the principal components of major depression: changes in 1/f slope have been shown to go along with hyperexcitability of infralimbic cortex in rodents, which in turn has been shown to cause impairment social interaction (Ferenczi et al., 2016). Assuming that slope changes between experimental conditions reflect changes in E/I balance, Veerakumar et al. (2019) tested patients with treatment-resistant depression and demonstrated, although in a very small sample, that right hemisphere slope changes could track sick/well states during ongoing SCC-DBS, with the match steeper slope – treatment response.
Semenova et al (2021) suggested a link between the abnormal head postures in patient with cervical dystonia and the asymmetry in the pallidal activity: the pallidum contralateral to the head-turning side appeared more inhibited than the ipsilateral side, showing thus a steeper slope; the 1/f slope was confirmed to be index of E/I balance, and abnormalities of this equilibrium was proposed as possible cause of a defective function of neural integration of the head movements.

Being a steeper slope generally associated with hypoexcitability (> GABA signaling and/or < Glutamate signaling) (Gao et al., 2017; Voytek et al., 2015), a flatter slope is associated with hyperexcitability (< GABA signaling and/or >glutamate signaling). Based on this assumption and on the results of the reviewed studies, we can divide most of the pathologies cited into two macro-groups in relation to the mechanism that reflects in slope alterations: i) hypo-excitability: ADHD, schizophrenia, Rett Syndrome, depression, cervical dystonia; ii) hyper-excitability: fragile X syndrome, Parkinson disease. It is interesting to note that three studies show counterintuitive findings: due to their pathophysiology, we expected ADHD and schizophrenia to be in the hyperexcitability group, and fragile X syndrome in the hypoexcitability one. On the contrary, the results show slope alterations that belong to the opposite group respectively. A possible explanation is thought to be the existence of compensation mechanisms, such as an increase in GABAergic activity in case of demanding tasks for patients who struggle with high cognitive control, or a decrease in GABAergic activity, aimed at normalizing firing rates, in patients with altered cortical spiking. Also, it has to be noted that while it might be appropriate to observe that pathologies affecting similar circuits or activities can show a similar pattern of spectral slope alterations, we do not have at this stage, enough evidence to proceed in the opposite direction, namely, to suppose that similar slope alterations necessary imply same mechanism underlying the examined diseases. We, again, would point out that the grouping we made is based on the results and the conclusions drawn by the authors and it should not be taken as definitive due to the huge heterogeneity of pathologies, techniques, sample size and, not the least, the still limited number of clinical studies.

We should although notice that at this early stage, the study of the aperiodic component of EEG power spectra is mostly challenging the current approach to EEG analysis and that the putative role of some features as biomarkers, together with the promising clinical applications, must be explored/confirmed by a larger number of analysis standardized in terms of methodological/technical approach. Several and relevant points related to 1/f should be discussed

and properly considered when interpreting any pathological changes. In particular, we would like to emphasize that 1/f may flatten as an effect of aging (Dave et al., 2018; Voytek et al., 2015) or may steepen in pharmacological induced unconsciousness (Colombo et al., 2019; Gao et al., 2017; Huang et al., 2020) or may discriminate between different states of consciousness (present/reduced or abolished) (Colombo et al., 2019). Moreover, 1/f slope has been shown to be a marker of states of reduced arousal, including sleep stages as well as anesthesia (Lendner et al., 2020; Miskovic et al., 2019; Muthukumaraswamy and Liley, 2018; Pereda et al., 1998; Shen et al., 2003).

Ultimately, persuaded of the clinical utility of the comprehensive approach to the features of EEG power spectra, we hope with this mini-review to boost the research about the aperiodic component of EEG signals in neurology and psychiatry. We aim to reach as many clinicians as we can and, through the summary proposed about versatility and possible applications of the aperiodic component analysis, promote use and scientific debate about it.

Author contribution

S.M. Pani: Conceptualization, Validation, Interpreting the relevant literature, Writing - original draft, Writing - review & editing.

M. Fraschini: Supervision, Interpreting the relevant literature, Writing – review & editing.

L. Saba: Writing – review & editing.

Founding sources

This work was supported by Regione Autonoma della Sardegna, L.R. 7/2007 annualità 2017 (Promozione della ricerca scientifica e dell'innovazione tecnologica in Sardegna - Risorse FSC 2014-2020 - Patto per lo Sviluppo della Regione Sardegna).

References

Al-Harbi KS. Treatment-resistant depression: Therapeutic trends, challenges, and future directions. Patient Prefer Adherence 2012;6:369–88. https://doi.org/10.2147/PPA.S29716.

Albanese A, Di Giovanni M, Lalli S. Dystonia: diagnosis and management. Eur J Neurol 2019;26:5–17. https://doi.org/10.1111/ene.13762.

Altamura AC, Fagiolini A, Galderisi S, Rocca P, Rossi A. Integrated treatment of schizophrenia. J Psychopathol 2015;21:168–93.

American Psychiatric Association. DSM-5 Diagnostic Classification. Diagnostic Stat. Man. Ment. Disord., 2013. https://doi.org/10.1176/appi.books.9780890425596.x00diagnosticclassification.

Armstrong MJ, Okun MS. Diagnosis and Treatment of Parkinson Disease: A Review. JAMA - J Am Med Assoc 2020;323:548–60. https://doi.org/10.1001/jama.2019.22360.

Arns M. EEG-Based Personalized Medicine in ADHD: Individual Alpha Peak Frequency as an Endophenotype Associated with Nonresponse. J Neurother 2012;16:123–41. https://doi.org/10.1080/10874208.2012.677664.

Arns M, Conners CK, Kraemer HC. A Decade of EEG Theta/Beta Ratio Research in ADHD: A Meta-Analysis. J Atten Disord 2013;17:374–83. https://doi.org/10.1177/1087054712460087.

Bak P, Tang C, Wiesenfeld K. Self-organized criticality: An explanation of the 1/f noise. Phys Rev Lett 1987;59:381–4. https://doi.org/10.1103/PhysRevLett.59.381.

Barbaresi WJ, Katusic SK, Voigt RG. Autism: A review of the state of the science for pediatric primary health care clinicians. Arch Pediatr Adolesc Med 2006;160:1167–75. https://doi.org/10.1001/archpedi.160.11.1167.

Barkley RA. Major life activity and health outcomes associated with attention-deficit/hyperactivity disorder. J Clin Psychiatry 2002;63:10–5.

Barry RJ, De Blasio FM. Characterizing pink and white noise in the human electroencephalogram. J Neural Eng 2021;18. https://doi.org/10.1088/1741-2552/abe399.

Batla A. Dystonia: A review. Neurol India 2018;66:S48–58. https://doi.org/10.4103/0028-3886.226439.

Bédard C, Kröger H, Destexhe A. Does the 1/f frequency scaling of brain signals reflect self-organized critical states? Phys Rev Lett 2006a;97. https://doi.org/10.1103/PhysRevLett.97.118102.

Bédard C, Kröger H, Destexhe A. Model of low-pass filtering of local field potentials in brain tissue. Phys Rev E - Stat Nonlinear, Soft Matter Phys 2006b;73. https://doi.org/10.1103/PhysRevE.73.051911.

Beggs JM. The criticality hypothesis: How local cortical networks might optimize information processing. Philos Trans R Soc A Math Phys Eng Sci 2008;366:329–43. https://doi.org/10.1098/rsta.2007.2092.

Belova EM, Semenova U, Gamaleya AA, Tomskiy AA, Sedov A. Voluntary movements cause beta oscillations increase and broadband slope decrease in the subthalamic nucleus of parkinsonian

patients. Eur J Neurosci 2021;53:2205–13. https://doi.org/10.1111/ejn.14715.

Bloem BR, Okun MS, Klein C. Parkinson's disease. Lancet 2021;397:2284–303. https://doi.org/10.1016/S0140-6736(21)00218-X.

Chen CC, Hsu YT, Chan HL, Chiou SM, Tu PH, Lee ST, et al. Complexity of subthalamic 13-35Hz oscillatory activity directly correlates with clinical impairment in patients with Parkinson's disease. Exp Neurol 2010;224:234–40. https://doi.org/10.1016/j.expneurol.2010.03.015.

Cohen MX. A neural microcircuit for cognitive conflict detection and signaling. Trends Neurosci 2014;37:480–90. https://doi.org/10.1016/j.tins.2014.06.004.

Colombo MA, Napolitani M, Boly M, Gosseries O, Casarotto S, Rosanova M, et al. The spectral exponent of the resting EEG indexes the presence of consciousness during unresponsiveness induced by propofol, xenon, and ketamine. Neuroimage 2019;189:631–44. https://doi.org/10.1016/j.neuroimage.2019.01.024.

Dave S, Brothers TA, Swaab TY. 1/F Neural Noise and Electrophysiological Indices of Contextual Prediction in Aging. Brain Res 2018;1691:34–43. https://doi.org/10.1016/j.brainres.2018.04.007.

Davie CA. A review of Parkinson's disease. Br Med Bull 2008;86:109–27. https://doi.org/10.1093/bmb/ldn013.

Demanuele C, James CJ, Sonuga-Barke EJS. Distinguishing low frequency oscillations within the 1/f spectral behaviour of electromagnetic brain signals. Behav Brain Funct 2007;3. https://doi.org/10.1186/1744-9081-3-62.

Demuru M, Fraschini M. EEG fingerprinting: Subject-specific signature based on the aperiodic component of power spectrum. Comput Biol Med 2020;120. https://doi.org/10.1016/j.compbiomed.2020.103748.

Demuru M, Gouw AA, Hillebrand A, Stam CJ, Van Dijk BW, Scheltens P, et al. Functional and effective whole brain connectivity using magnetoencephalography to identify monozygotic twin pairs. Sci Rep 2017;7. https://doi.org/10.1038/s41598-017-10235-y.

Derry CP, Davey M, Johns M, Kron K, Glencross D, Marini C, et al. Distinguishing sleep disorders from seizures: Diagnosing bumps in the night. Arch Neurol 2006;63:705–9. https://doi.org/10.1001/archneur.63.5.705.

Donoghue T. #AcademicEEG -Twitter. Twitter 2020. https://twitter.com/Tomdonoghue/status/1356653760517464069.

Donoghue T, Dominguez J, Voytek B. Electrophysiological frequency band ratio measures conflate periodic and aperiodic neural activity. ENeuro 2020a;7. https://doi.org/10.1523/ENEURO.0192-20.2020.

Donoghue T, Haller M, Peterson EJ, Varma P, Sebastian P, Gao R, et al. Parameterizing neural power spectra into periodic and aperiodic components. Nat Neurosci 2020b;23:1655–65. https://doi.org/10.1038/s41593-020-00744-x.

Donoghue T, Schaworonkow N, Voytek B. Methodological considerations for studying neural oscillations. Eur J Neurosci 2021. https://doi.org/10.1111/ejn.15361.

Doyle JA, Evans AC. What Colour is Neural Noise? 2018 Conf Cogn Comput Neurosci 2018. https://doi.org/arXiv:1806.03704v1.

Ethridge LE, De Stefano LA, Schmitt LM, Woodruff NE, Brown KL, Tran M, et al. Auditory EEG Biomarkers in Fragile X Syndrome: Clinical Relevance. Front Integr Neurosci 2019;13. https://doi.org/10.3389/fnint.2019.00060.

Fahn S, Bressman SB, Marsden CD. Classification of dystonia. Adv Neurol 1998;78:1–10. https://doi.org/10.2217/ebo.13.168.

Ferenczi EA, Zalocusky KA, Liston C, Grosenick L, Warden MR, Amatya D, et al. Prefrontal cortical regulation of brainwide circuit dynamics and reward-related behavior. Science (80-) 2016. https://doi.org/10.1126/science.aac9698.

Fraschini M, Hillebrand A, Demuru M, Didaci L, Marcialis GL. An EEG-based biometric system using eigenvector centrality in resting state brain networks. IEEE Signal Process Lett 2015;22:666–70. https://doi.org/10.1109/LSP.2014.2367091.

Freeman WJ. Origin, structure, and role of background EEG activity. Part 4: Neural frame simulation. Clin Neurophysiol 2006;117:572–89. https://doi.org/10.1016/j.clinph.2005.10.025.

Freeman WJ. Origin, structure, and role of background EEG activity. Part 3. Neural frame classification. Clin Neurophysiol 2005;116:1118–29. https://doi.org/10.1016/j.clinph.2004.12.023.

Freeman WJ. Origin, structure, and role of background EEG activity. Part 1. Analytic amplitude. Clin Neurophysiol 2004a;115:2077–88. https://doi.org/10.1016/j.clinph.2004.02.029.

Freeman WJ. Origin, structure, and role of background EEG activity. Part 2. Analytic phase. Clin Neurophysiol 2004b;115:2089–107. https://doi.org/10.1016/j.clinph.2004.02.028.

Gao R synaptic excitation/inhibition balance from field potentials, Peterson EJ, Voytek B. Inferring synaptic excitation/inhibition balance from field potentials. Neuroimage 2017;158:70–8. https://doi.org/10.1016/j.neuroimage.2017.06.078.

Greenblatt DW. The International Classification of Sleep Disorders. vol. 49. 1992. https://doi.org/10.1001/archneur.1992.00530270020006.

Hagerman RJ, Berry-Kravis E, Hazlett HC, Bailey DB, Moine H, Kooy RF, et al. Fragile X syndrome. Nat Rev Dis Prim 2017;3:17065. https://doi.org/10.1038/nrdp.2017.65.

Hagerman RJ, Berry-Kravis E, Kaufmann WE, Ono MY, Tartaglia N, Lachiewicz A, et al. Advances in the treatment of fragile x Syndrome. Pediatrics 2009;123:378–90. https://doi.org/10.1542/peds.2008-0317.

Hammond C, Bergman H, Brown P. Pathological synchronization in Parkinson's disease: networks, models and treatments. Trends Neurosci 2007;30:357–64. https://doi.org/10.1016/j.tins.2007.05.004.

He BJ. Scale-free brain activity: Past, present, and future. Trends Cogn Sci 2014;18:480–7. https://doi.org/10.1016/j.tics.2014.04.003.

He BJ, Zempel JM, Snyder AZ, Raichle ME. The temporal structures and functional significance of scale-free brain activity. Neuron 2010;66:353–69. https://doi.org/10.1016/j.neuron.2010.04.020.

Hesse J, Gross T. Self-organized criticality as a fundamental property of neural systems. Front Syst Neurosci 2014;8. https://doi.org/10.3389/fnsys.2014.00166.

Hoffmann H, Payton DW. Optimization by Self-Organized Criticality. Sci Rep 2018;8. https://doi.org/10.1038/s41598-018-20275-7.

Hrozanova M, Morrison I, Riha R. Adult NREM Parasomnias: An Update. Clocks & Sleep 2018;1:87–104. https://doi.org/10.3390/clockssleep1010009.

Huang Y, Hu K, Green AL, Ma X, Gillies MJ, Wang S, et al. Dynamic changes in rhythmic and arrhythmic neural signatures in the subthalamic nucleus induced by anaesthesia and tracheal intubation. Br J Anaesth 2020;125:67–76. https://doi.org/10.1016/j.bja.2020.03.014.

Ip JPK, Mellios N, Sur M. Rett syndrome: Insights into genetic, molecular and circuit mechanisms. Nat Rev Neurosci 2018;19:368–82. https://doi.org/10.1038/s41583-018-0006-3.

Iturrate I, Pereira M, Millán J del R. Closed-loop electrical neurostimulation: Challenges and opportunities. Curr Opin Biomed Eng 2018;8:28–37. https://doi.org/10.1016/j.cobme.2018.09.007.

Ben Itzchak E, Zachor DA. Who benefits from early intervention in autism spectrum disorders? Res Autism Spectr Disord 2011;5:345–50. https://doi.org/10.1016/j.rasd.2010.04.018.

Kalia L V., Lang AE. Parkinson's disease. Lancet 2015;386:896–912. https://doi.org/10.1016/S0140-6736(14)61393-3.

Kosciessa JQ, Grandy TH, Garrett DD, Werkle-Bergner M. Single-trial characterization of neural rhythms: Potential and challenges. Neuroimage 2020;206. https://doi.org/10.1016/j.neuroimage.2019.116331.

Kouli A, Torsney KM, Kuan W-L. Parkinson's Disease: Etiology, Neuropathology, and Pathogenesis. Park. Dis. Pathog. Clin. Asp., 2018, p. 3–26. https://doi.org/10.15586/codonpublications.parkinsonsdisease.2018.ch1.

Lanzone J, Colombo M, Sarasso S, Zappasodi F, Rosanova M, Massimini M, et al. EEG spectral exponent as a synthetic index for the longitudinal assessment of stroke recovery. BioRxiv 2021:2021.08.09.455664. https://doi.org/https://doi.org/10.1101/2021.08.09.455664.

Lendner JD, Helfrich RF, Mander BA, Romundstad L, Lin JJ, Walker MP, et al. An electrophysiological marker of arousal level in humans. Elife 2020;9:1–29. https://doi.org/10.7554/eLife.55092.

Lenroot R, Bustillo JR, Lauriello J, Keith SJ. Integrated Treatment of Schizophrenia. Psychiatr Serv 2003;54:1499–507. https://doi.org/10.1176/appi.ps.54.11.1499.

Levin AR, Naples AJ, Scheffler AW, Webb SJ, Shic F, Sugar CA, et al. Day-to-Day Test-Retest Reliability of EEG Profiles in Children With Autism Spectrum Disorder and Typical Development. Front Integr Neurosci 2020;14. https://doi.org/10.3389/fnint.2020.00021.

Lewis DA, Hashimoto T, Volk DW. Cortical inhibitory neurons and schizophrenia. Nat Rev Neurosci 2005;6:312–24. https://doi.org/10.1038/nrn1648.

Lindén H, Pettersen KH, Einevoll GT. Intrinsic dendritic filtering gives low-pass power spectra of

local field potentials. J Comput Neurosci 2010;29:423–44. https://doi.org/10.1007/s10827-010-0245-4.

Lubar JF. Discourse on the development of EEG diagnostics and biofeedback for attention-deficit/hyperactivity disorders. Biofeedback Self Regul 1991;16:201–25. https://doi.org/10.1007/BF01000016.

Malhi GS, Mann JJ. Depression. Lancet 2018;392:2299–312. https://doi.org/10.1016/S0140-6736(18)31948-2.

Marsili L, Rizzo G, Colosimo C. Diagnostic criteria for Parkinson's disease: From James Parkinson to the concept of prodromal disease. Front Neurol 2018;9. https://doi.org/10.3389/fneur.2018.00156.

Martin S, Iturrate I, Chavarriaga R, Leeb R, Sobolewski A, Li AM, et al. Differential contributions of subthalamic beta rhythms and 1/f broadband activity to motor symptoms in Parkinson's disease. Npj Park Dis 2018;4. https://doi.org/10.1038/s41531-018-0068-y.

Miller JL. Parkinson's disease primer. Geriatr Nurs (Minneap) 2002;23:69–75. https://doi.org/10.1067/mgn.2002.123789.

Miller KJ, Sorensen LB, Ojemann JG, Den Nijs M. Power-law scaling in the brain surface electric potential. PLoS Comput Biol 2009;5. https://doi.org/10.1371/journal.pcbi.1000609.

Miskovic V, MacDonald KJ, Rhodes LJ, Cote KA. Changes in EEG multiscale entropy and power-law frequency scaling during the human sleep cycle. Hum Brain Mapp 2019;40:538–51. https://doi.org/10.1002/hbm.24393.

Molina JL, Voytek B, Thomas ML, Joshi YB, Bhakta SG, Talledo JA, et al. Memantine Effects on Electroencephalographic Measures of Putative Excitatory/Inhibitory Balance in Schizophrenia. Biol Psychiatry Cogn Neurosci Neuroimaging 2020;5:562–8. https://doi.org/10.1016/j.bpsc.2020.02.004.

Moll CKE, Galindo-Leon E, Sharott A, Gulberti A, Buhmann C, Koeppen JA, et al. Asymmetric pallidal neuronal activity in patients with cervical dystonia. Front Syst Neurosci 2014;8. https://doi.org/10.3389/fnsys.2014.00015.

Motokawa K. Energy of Brain Waves and Energetics of the Brain. Tohoku J Exp Med 1949;51:119–29. https://doi.org/10.1620/tjem.51.119.

Muthukumaraswamy SD, Liley DT. 1/F Electrophysiological Spectra in Resting and Drug-Induced States Can Be Explained By the Dynamics of Multiple Oscillatory Relaxation Processes. Neuroimage 2018;179:582–95. https://doi.org/10.1016/j.neuroimage.2018.06.068.

Neul JL, Kaufmann WE, Glaze DG, Christodoulou J, Clarke AJ, Bahi-Buisson N, et al. Rett syndrome: Revised diagnostic criteria and nomenclature. Ann Neurol 2010;68:944–50. https://doi.org/10.1002/ana.22124.

Niedermeyer E, Rett A, Renner H. Rett syndrome and the electroencephalogram. Am J Med Genet 1986;24:195–9. https://doi.org/10.1002/ajmg.1320250522.

Owen MJ, Sawa A, Mortensen PB. Schizophrenia. Lancet 2016;388:86–97.

https://doi.org/10.1016/S0140-6736(15)01121-6.

Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. BMJ 2021;372. https://doi.org/10.1136/bmj.n71.

Palva S, Palva JM. Roles of Brain Criticality and Multiscale Oscillations in Temporal Predictions for Sensorimotor Processing. Trends Neurosci 2018;41:729–43. https://doi.org/10.1016/j.tins.2018.08.008.

Pani SM, Ciuffi M, Demuru M, La Cava SM, Bazzano G, D'Aloja E, et al. Subject, session and task effects on power, connectivity and network centrality: A source-based EEG study. Biomed Signal Process Control 2020;59. https://doi.org/10.1016/j.bspc.2020.101891.

Pani SM, Fraschini M, Figorilli M, Tamburrino L, Ferri R, Puligheddu M. Sleep-related hypermotor epilepsy and non-rapid eye movement parasomnias: Differences in the periodic and aperiodic component of the electroencephalographic power spectra. J Sleep Res 2021;30. https://doi.org/10.1111/jsr.13339.

Park HR, Lee JM, Moon HE, Lee DS, Kim BN, Kim J, et al. A short review on the current understanding of autism spectrum disorders. Exp Neurobiol 2016;25:1–13. https://doi.org/10.5607/en.2016.25.1.1.

Pereda E, Gamundi A, Rial R, González J. Non-linear behaviour of human EEG: Fractal exponent versus correlation dimension in awake and sleep stages. Neurosci Lett 1998;250:91–4. https://doi.org/10.1016/S0304-3940(98)00435-2.

Pertermann M, Bluschke A, Roessner V, Beste C. The Modulation of Neural Noise Underlies the Effectiveness of Methylphenidate Treatment in Attention-Deficit/Hyperactivity Disorder. Biol Psychiatry Cogn Neurosci Neuroimaging 2019;4:743–50. https://doi.org/10.1016/j.bpsc.2019.03.011.

Peterson E, Rosen B, Campbell A, Belger A, Voytek B. 1/ F Neural Noise Is a Better Predictor of Schizophrenia Than Neural Oscillations. BioRxiv 2017:113449. https://doi.org/10.1101/113449.

Pettersen KH, Lindén H, Tetzlaff T, Einevoll GT. Power Laws from Linear Neuronal Cable Theory: Power Spectral Densities of the Soma Potential, Soma Membrane Current and Single-Neuron Contribution to the EEG. PLoS Comput Biol 2014;10. https://doi.org/10.1371/journal.pcbi.1003928.

Podvalny E, Noy N, Harel M, Bickel S, Chechik G, Schroeder CE, et al. A unifying principle underlying the extracellular field potential spectral responses in the human cortex. J Neurophysiol 2015;114:505–19. https://doi.org/10.1152/jn.00943.2014.

Popa T, Hubsch C, James P, Richard A, Russo M, Pradeep S, et al. Abnormal cerebellar processing of the neck proprioceptive information drives dysfunctions in cervical dystonia. Sci Rep 2018;8. https://doi.org/10.1038/s41598-018-20510-1.

Posner J, Polanczyk G V., Sonuga-Barke E. Attention-deficit hyperactivity disorder. Lancet 2020;395:450–62. https://doi.org/10.1016/S0140-6736(19)33004-1.

Pritchard WS. The brain in fractal time: 1/f-like power spectrum scaling of the human

electroencephalogram. Int J Neurosci 1992;66:119–29. https://doi.org/10.3109/00207459208999796.

Ray NJ, Jenkinson N, Wang S, Holland P, Brittain JS, Joint C, et al. Local field potential beta activity in the subthalamic nucleus of patients with Parkinson's disease is associated with improvements in bradykinesia after dopamine and deep brain stimulation. Exp Neurol 2008;213:108–13. https://doi.org/10.1016/j.expneurol.2008.05.008.

Robertson MM, Furlong S, Voytek B, Donoghue T, Boettiger CA, Sheridan MA. EEG power spectral slope differs by ADHD status and stimulant medication exposure in early childhood. J Neurophysiol 2019;122:2427–37. https://doi.org/10.1152/jn.00388.2019.

Robinson PA, Rennie CJ, Wright JJ, Bahiumuli H, Gordon E, Rowe DL. Prediction of electrocnccphulographic spectra from neurophysiology. Phys Rev E - Stat Nonlinear, Soft Matter Phys 2001;63:0219031–02190318. https://doi.org/10.1103/PhysRevE.63.021903.

Rocca D La, Campisi P, Vegso B, Cserti P, Kozmann G, Babiloni F, et al. Human brain distinctiveness based on EEG spectral coherence connectivity. IEEE Trans Biomed Eng 2014;61:2406–12. https://doi.org/10.1109/TBME.2014.2317881.

Roche KJ, Leblanc JJ, Levin AR, O'Leary HM, Baczewski LM, Nelson CA. Electroencephalographic spectral power as a marker of cortical function and disease severity in girls with Rett syndrome. J Neurodev Disord 2019;11. https://doi.org/10.1186/s11689-019-9275-z.

Rogers SJ, Vismara LA. Evidence-based comprehensive treatments for early autism. J Clin Child Adolesc Psychol 2008;37:8–38. https://doi.org/10.1080/15374410701817808.

Sakurai T, Gamo NJ, Hikida T, Kim SH, Murai T, Tomoda T, et al. Converging models of schizophrenia - Network alterations of prefrontal cortex underlying cognitive impairments. Prog Neurobiol 2015;134:178–201. https://doi.org/10.1016/j.pneurobio.2015.09.010.

Samaha J, Cohen MX. Power spectrum slope confounds estimation of instantaneous oscillatory frequency. Neuroimage 2022;250:118929. https://doi.org/10.1016/j.neuroimage.2022.118929.

Schaworonkow N, Voytek B. Longitudinal changes in aperiodic and periodic activity in electrophysiological recordings in the first seven months of life. Dev Cogn Neurosci 2021;47. https://doi.org/10.1016/j.dcn.2020.100895.

Sedov A, Semenova U, Usova S, Tomskiy A, Crawford JD, Jinnah HA, et al. Implications of asymmetric neural activity patterns in the basal ganglia outflow in the integrative neural network model for cervical dystonia. Prog. Brain Res., vol. 249, 2019a, p. 261–8. https://doi.org/10.1016/bs.pbr.2019.03.030.

Sedov A, Usova S, Semenova U, Gamaleya A, Tomskiy A, Crawford JD, et al. The role of pallidum in the neural integrator model of cervical dystonia. Neurobiol Dis 2019b;125:45–54. https://doi.org/10.1016/j.nbd.2019.01.011.

Semenova U, Popov V, Tomskiy A, Shaikh AG, Sedov A. Pallidal 1/f asymmetry in patients with cervical dystonia. Eur J Neurosci 2021;53:2214–9. https://doi.org/10.1111/ejn.14729.

Sheehan TC, Sreekumar V, Inati SK, Zaghloul KA. Signal complexity of human intracranial EEG tracks successful associative-memory formation across individuals. J Neurosci 2018;38:1744–55.

https://doi.org/10.1523/JNEUROSCI.2389-17.2017.

Shen Y, Olbrich E, Achermann P, Meier PF. Dimensional complexity and spectral properties of the human sleep EEG. Clin Neurophysiol 2003;114:199–209. https://doi.org/10.1016/S1388-2457(02)00338-3.

Stadnitski T. Measuring fractality. Front Physiol 2012;3 MAY. https://doi.org/10.3389/fphys.2012.00127.

Stam CJ. Modern network science of neurological disorders. Nat Rev Neurosci 2014;15:683–95. https://doi.org/10.1038/nrn3801.

Tran TT, Rolle CE, Gazzaley A, Voytek B. Linked sources of neural noise contribute to age-related cognitive decline. J Cogn Neurosci 2020;32:1813–22. https://doi.org/10.1162/jocn_a_01584.

Uhlhaas PJ, Singer W. Oscillations and neuronal dynamics in schizophrenia: The search for basic symptoms and translational opportunities. Biol Psychiatry 2015;77:1001–9. https://doi.org/10.1016/j.biopsych.2014.11.019.

Veerakumar A, Tiruvadi V, Howell B, Waters AC, Crowell AL, Voytek B, et al. Field potential 1/f activity in the subcallosal cingulate region as a candidate signal for monitoring deep brain stimulation for treatment-resistant depression. J Neurophysiol 2019;122:1023–35. https://doi.org/10.1152/jn.00875.2018.

Voytek B, Knight RT. Dynamic network communication as a unifying neural basis for cognition, development, aging, and disease. Biol Psychiatry 2015;77:1089–97. https://doi.org/10.1016/j.biopsych.2015.04.016.

Voytek B, Kramer MA, Case J, Lepage KQ, Tempesta ZR, Knight RT, et al. Age-related changes in 1/f neural electrophysiological noise. J Neurosci 2015;35:13257–65. https://doi.org/10.1523/JNEUROSCI.2332-14.2015.

Wang J, Barstein J, Ethridge LE, Mosconi MW, Takarae Y, Sweeney JA. Resting state EEG abnormalities in autism spectrum disorders. J Neurodev Disord 2013;5. https://doi.org/10.1186/1866-1955-5-24.

Wang J, Ethridge LE, Mosconi MW, White SP, Binder DK, Pedapati E V., et al. A resting EEG study of neocortical hyperexcitability and altered functional connectivity in fragile X syndrome Refining translational treatment development in fragile X syndrome. J Neurodev Disord 2017;9. https://doi.org/10.1186/s11689-017-9191-z.

Ward LM, Greenwood PE. 1/f noise. Scholarpedia 2007:2(12):1537. https://doi.org/10.4249/scholarpedia.1537.

Wen H, Liu Z. Separating Fractal and Oscillatory Components in the Power Spectrum of Neurophysiological Signal. Brain Topogr 2016;29:13–26. https://doi.org/10.1007/s10548-015-0448-0.

Wilkinson CL, Nelson CA. Increased aperiodic gamma power in young boys with Fragile X Syndrome is associated with better language ability. Mol Autism 2021;12. https://doi.org/10.1186/s13229-021-00425-x.

Williamson PO, Minter CIJ. Exploring PubMed as a reliable resource for scholarly communications services. J Med Libr Assoc 2019;107:16–29. https://doi.org/10.5195/jmla.2019.433.

Zhang DW, Roodenrys S, Li H, Barry RJ, Clarke AR, Wu Z, et al. Atypical interference control in children with AD/HD with elevated theta/beta ratio. Biol Psychol 2017;128:82–8. https://doi.org/10.1016/j.biopsycho.2017.07.009.