様　式　Ｃ－１９、Ｆ－１９－１、Ｚ－１９　（共通）

# 科学研究費助成事業　　研究成果報告書

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研究課題名（和文）過渡的事象に注目した新規解析手法による睡眠脳波の解析

研究課題名（英文）Sleep EEG diagnosis through novel method sensitive to phasic events

研究代表者
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交付決定額（研究期間全体）：（直接経費）　 3,400,000円

研究成果の概要（和文）：(これはドラフトであり、実際のレポートは後日再提出されます。)
不整脈パルスの重ね合わせから生じる信号の計算モデルから、パルスを記述する関数と出現する波の重ね合わせの自己共分散関数をリンクする基本的な数学的関係を発見しました。 異なるパルスの混合を含む重ね合わせの場合、私たちの方法の応答は、タウ= 0（すなわち、自己共分散分析の原点）に整列され、それらのエネルギー寄与に従ってスケーリングされた個々のパルスの線形重ね合わせをもたらします。

研究成果の学術的意義や社会的意義
EEG is a powerful tool for scientific research, medical diagnosis, and the development of brain-computer interfaces. This research aims to resolve fundamental open questions about the origin of EEG. Learning to extract EEG features directly linked to its ontology will greatly enhance its usefulness.

研究成果の概要（英文）：Starting from computational models of signals arising from a superposition of arrhythmic pulses, we discovered a fundamental mathematical relationship linking the function describing the pulse and the auto-covariance function of the emerging wave superposition. For a superposition involving a mixture of different pulses, the response of the method corresponds to the linear superposition of individual pulses aligned at tau=0 (i.e. auto-covariance analysis origin) and scaled in accordance with their energy contribution. Applied to EEG, the technique reveals unique patterns characterizing NREM sleep, REM sleep, active wake, and grooming behavior. Remarkably, the method allows, for the first time, the detection of an EEG feature specific to wakefulness. From a theoretic perspective, these results strongly support the view that EEG arises mainly from arrhythmic (phasic) neuronal activity.

研究分野：Life, Health and Medical Informatics Related

キーワード：Sleep physiology　Sleep mutants　Envelope analysis　EEG　Human Polysomnography　Random Walk　Time‐domain‐analysis　Computer simulations

## １．研究開始当初の背景

After almost a century of development, electroencephalography (EEG) is well established as an important scientific tool for research and clinical practice. For instance, clear distinctions between normal and pathological EEG patterns allow the diagnosis of epilepsy (and other seizure disorders), brain damage (tumor, trauma, inflammation), and sleep disorders, among other conditions.

Despite a long history of EEG and its indisputable utility and promising projections in several domains, the interpretation of EEG patterns still poses fundamental questions. The standard interpretation of EEG relies heavily on descriptions in the frequency domain (mainly using Fourier analysis), where most of the signal power is interpreted as generated from the synchronization of neuronal oscillators at different frequency bands. However, these mainstream ideas are challenged by views considering a prominent arrhythmic EEG nature mainly reflected in the 1/f structure of the EEG spectrum.

## ２．研究の目的

Hypothesizing that EEG mainly originates from arrhythmic neuronal activity, this study aims to explore the mathematical properties of an arrhythmic superposition of pulses (phasic neuronal activity) in order to eventually identify these properties in actual EEG. Understanding the genesis of EEG will allow the extraction of features directly reflecting its ontology. This, in turn, will improve the usability of EEG as a scientific research tool, medical diagnosis, and the development of EEG-based technology in general (e.g. brain-machine interfaces).

## ３．研究の方法

**EEG/EMG surgery (mouse).** Electrode implantation for standard mice EEG recording was carried out as described in doi:10.1038/nature20142. **EEG/EMG recordings.** EEG an EMG were acquired at 5kHz using INTAN systems hardware and stored for off-line analysis. **Superposition of pulses (computer simulations)** Signals were constructed by the convolution between pulses defined by arbitrary functions (e.g. square pulse, alpha function, etc.) and a vector composed by Kronecker deltas following a Poisson process with pulse density $\lambda$.**EEG transient analysis.** Numerical calculations related to the novel method will kept confidential at this time.

## ４．研究成果

EEG can be conceptualized as a superposition of pulses. Let us consider a simple stochastic process $X$ originated from the arrhythmic superposition of pulses defined by the arbitrary function $g(t)$, $X = \Sigma\, g(t + t_j)$. These pulses carry a finite amount of energy $E_g$. The time occurrence of each pulse $(t_j)$ is determined by an homogeneous Poisson process with parameter $\lambda_g$ controlling events per second.

Black traces in figure 1A illustrate a sequence of stochastic superposition $X$ with an increasing number of pulses. When the density of pulses $\lambda_g$ (i.e. pulses per second) is high,the shape of $g(t)$ cannot be recognized within the emerging random patterns. Figure 1B show the spectral properties (pink) of process X (light-blue) as a function of the underlying pulse (yellow), an alpha function of $\tau$ = 2,4,8,16, and 32 ms (from top to bottom). Notice that when the pulse is wide, the spectral power is concentrated in the lower frequencies (a phenomenon originated from an arrhythmic process). Figure 1C shows the stationarity of process X illustrated by the constant amplitude (red trace is the standard deviation computed from 5000 instances of the process). Figure 1D shows a collection of processes generated in equal conditions as in C, the signals are translated to zero at the arbitrary time $t_0$ (vertical dotted line), by subtracting $X(t_0)$. The amplitude of the random process after this translation grows from zero in a constrained fashion. The red trace is the standard deviation calculated over 5000 instances of the translated process (X_hat), describing the temporal profile of this diffusion. The fundamental result of this study corresponds to the mathematical relationship (and its mathematical proof) connecting the red curve and the blue curve (underlying pulse). From this relationship, the pulse or mixture of pulses) can be inferred from a complex signal (e.g. EEG).

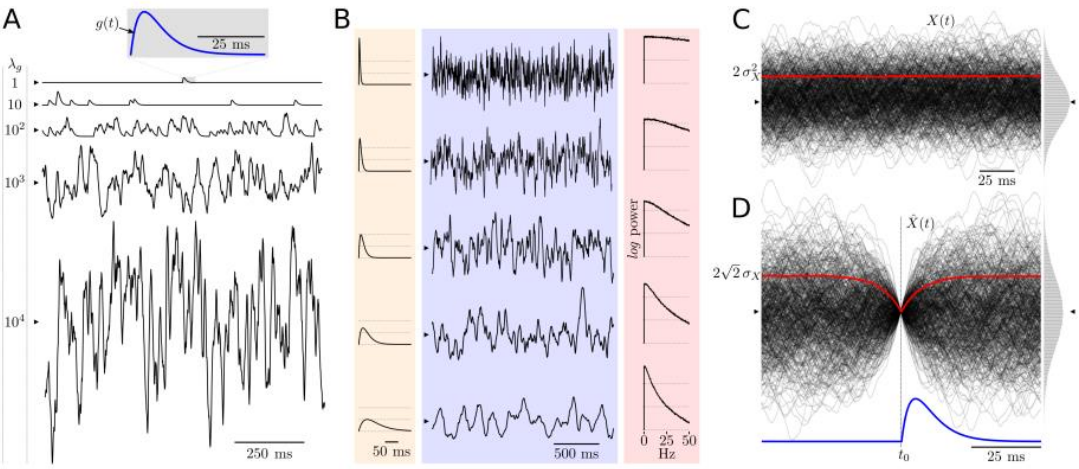

FIGURE 1

Figure 2 illustrates the novel EEG features provided by the analysis. Figure 2A shows the hypnogram corresponding to a representative one-hour mouse spontaneous EEG recording (R = REM sleep, N = non-REM sleep, W = wakefulness). Figure 2B shows the multitaper spectrum of the same EEG segment (pseudo-color represents log-spectral power, black < blue < cyan < orange < red < dark-red). Figure 2C shows a heatmap built from the novel EEG features giving a new perspective to brain dynamics. Figure 2D shows spectra representative of wakefulness (gray), REM sleep (red) and non-REM sleep (blue), corresponding to the 100-second segments highlighted by rectangles similarly colored in panels A, B and C. Figure 2 E-F shows the new EEG features corresponding to the same 100-second segments.

These new EEG features are less noisy than classic Fourier-based spectral features, exhibiting a richer morphology with unique patterns characterizing every behavioral state. Remarkably, using these features it is possible to classify behavioral states using only EEG (not requiring EMG). Clustering of behavioral states based on principal component analysis is not shown.

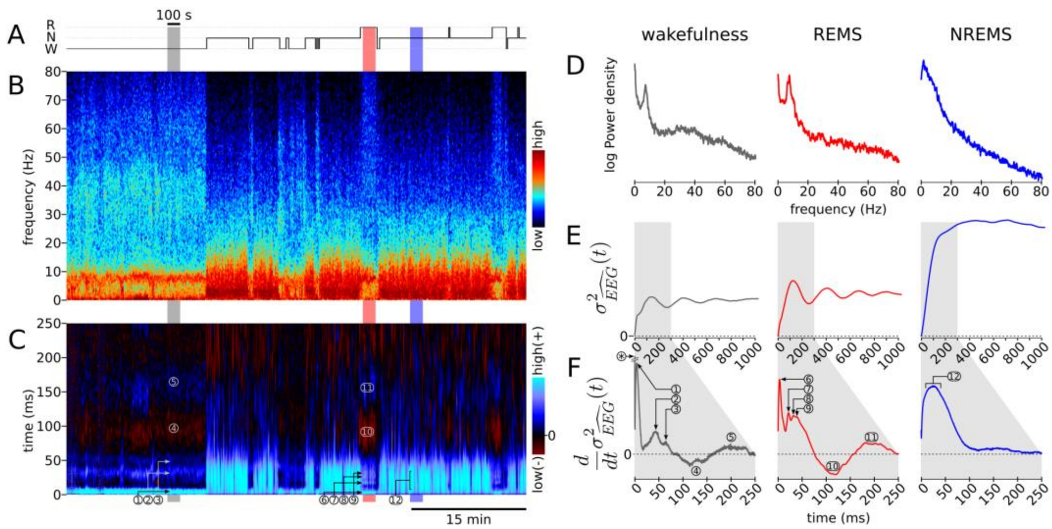


FIGURE 2

５．主な発表論文等

〔雑誌論文〕　計1件（うち査読付論文　1件／うち国際共著　1件／うちオープンアクセス　1件）

| | |
|---|---|
| １．著者名<br>Insung Park*, Javier Diaz*, Sumire Matsumoto, Kaito Iwayama, Yoshiharu Nabekura, Hitomi Ogata, Momoko Kayaba, Atsushi Aoyagi, Katsuhiko Yajima, Makoto Satoh, Kumpei Tokuyama, Kaspar E Vogt | ４．巻<br>11 |
| ２．論文標題<br>Exercise improves the quality of slow-wave sleep by increasing slow-wave stability | ５．発行年<br>2021年 |
| ３．雑誌名<br>Scientific Reports | ６．最初と最後の頁<br>4410 |
| 掲載論文のDOI（デジタルオブジェクト識別子）<br>10.1038/s41598-021-83817-6 | 査読の有無<br>有 |
| オープンアクセス<br>オープンアクセスとしている（また、その予定である） | 国際共著<br>該当する |

〔学会発表〕　計3件（うち招待講演　0件／うち国際学会　3件）

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|---|
| １．発表者名<br>J. Diaz , H. Funato, J.-C. Letelier, M. Yanagisawa, and K.E. Vogt |
| ２．発表標題<br>Electroencephalographic characterization of the Sleepy mutant reveals a multi-spectral disorganization of NREM sleep dynamics accompanied by absence of active wakefulness markers |
| ３．学会等名<br>Neuro2019, Japanese Neuroscience Society（国際学会） |
| ４．発表年<br>2019年 |

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|---|
| １．発表者名<br>Diaz J, Matsumoto S, Oyama K and Vogt KE |
| ２．発表標題<br>Temporal and spectral properties of mouse cortical LFP explained from a conceptual framework based on transient events |
| ３．学会等名<br>IBRO 2019（国際学会） |
| ４．発表年<br>2019年 |

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| １．発表者名<br>Insung Park, Javier Diaz, Sumire Matsumoto, Kaito Iwayama, Yoshiharu Nabekura, Hitomi Ogata, Momoko Kayaba, Makoto Satoh, Kumpei Tokuyama |
| ２．発表標題<br>Exercise modifies mathematical properties of δ-power: the envelope analysis |
| ３．学会等名<br>World Sleep 2019（国際学会） |
| ４．発表年<br>2019年 |

〔図書〕　計0件

〔産業財産権〕

〔その他〕

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6．研究組織

| | 氏名<br>（ローマ字氏名）<br>（研究者番号） | 所属研究機関・部局・職<br>（機関番号） | 備考 |
|---|---|---|---|
| 研究分担者 | 佐藤　誠<br>(Diaz Javier)<br>(50242409) | 筑波大学・国際統合睡眠医科学研究機構・教授<br>(12102) | |

7．科研費を使用して開催した国際研究集会

〔国際研究集会〕　計0件

8．本研究に関連して実施した国際共同研究の実施状況

| 共同研究相手国 | 相手方研究機関 |
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