Does the Brain's E/I Balance Really Shape Long-Range Temporal Correlations?

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Abstract

A 3T multimodal MRI study of healthy adults (n=19; 10 female; 21-54 years) was performed to investigate the potential link between fMRI long-range temporal correlations and excitatory/inhibitory balance. The study objective was to determine if the Hurst exponent (HE) – an estimate of the self-correlation and signal complexity of the blood-oxygen-level-dependent (BOLD) signal – is correlated with the excitatory-inhibitory (E/I) ratio. Findings in this domain have implications for neurological and neuropsychiatric conditions with disrupted E/I balance, such as autism spectrum disorder, schizophrenia, and Alzheimer's disease. From a methodological perspective, HE

is also considerably easier to accurately measure than E/I ratio. If HE can serve as a proxy for E/I, it may serve as a useful clinical biomarker for E/I imbalance. Moreover, E/I has been proposed to serve as a control parameter for brain criticality, which HE is believed to be a measure of. Thus, understanding if HE and E/I are correlated would serve to clarify this relationship. The study collected movie-watching and rest data including fMRI – which was used to calculate HE – and magnetic resonance spectroscopy (MRS) – which was used to measure inhibitory and excitatory neurotransmitters – GABA and glutamate, respectively. HE was found to increase with movie compared to rest, while E/I did not change between conditions. HE and E/I were not correlated during either movie or rest. This study represents the first attempt to investigate this connection *in vivo* in humans. We conclude that, at 3T and with our particular methodologies, no association was found.

Introduction

Thirty years ago, functional magnetic resonance imaging (fMRI) profoundly changed the world of MRI by allowing real-time analysis of pressing neuropsychological questions [Ogawa and Lee, 1990, Ogawa et al., 1990, Stephan and Roebroeck, 2012]. While initially used to probe task-based responses, researchers have more recently developed an interest in studying brain function at rest, known as resting-state fMRI (rs-fMRI) [Deco et al., 2013], i.e. to understand how brain dynamics at rest are related to neurological functioning as well as individual differences. A critical tool in analyzing these dynamics is the Hurst exponent (HE) [Campbell and Weber, 2022], a measure of self-similarity derived from the blood-oxygen-dependent (BOLD) signal. HE estimates the extent to which the BOLD signal displays long-term memory, where a higher value indicates a self-similar signal with long-term positive autocorrelations [Campbell and Weber, 2022, Beggs and Timme, 2012]. Another way of understanding HE is that a signal with high HE is fractal: similar temporal signal fluctuations are observed, no matter the time scale [Campbell and Weber, 2022].

HE has also emerged as a valuable tool in clinical research, capturing changes in BOLD signal dynamics across various neuropsychiatric conditions. In aging populations for instance, HE has been found to be elevated [Dong et al., 2018, Wink et al., 2006]; this relationship has also been found in mild cognitive impairment and Alzheimer's disease [Maxim et al., 2005, Long et al., 2018]. Additionally, changes in HE have been observed in conditions such as autism, mood disorders, and brain injury [Lai et al., 2010, Dona et al., 2017a, Wei et al., 2013, Jing et al., 2017, Dona et al., 2017b]. These differences suggest HE may reflect changes in global and local functioning.

Underlying these observations is the critical brain hypothesis, which posits that the brain operates at a critical point, a state where order and disorder are perfectly balanced to enable optimal information processing [Deco et al., 2013, Beggs and Timme, 2012, Baranger, 2000, Bassett and Gazzaniga, 2011, Zimmern, 2020, Liang et al., 2024, Poil et al., 2012, Lombardi et al., 2017, Baumgarten and Bornholdt, 2019, Bruining et al., 2020, Trakoshis et al., Gao et al., 2017, Tian et al., 2022, Rubinov et al., 2011]. When operating at a critical point, the brain is maximally sensitive to external stimuli, and can dynamically transition between ordered and disordered states to promote efficient cognitive processing [Deco et al., 2013, Beggs and Timme, 2012, Tian et al., 2022, Rubinov et al., 2011].Recent papers suggest the control parameter underlying the brain's ability to transition between states is the excitatory-inhibitory (E/I) ratio, the balance of excitatory and inhibitory neural activity, often operationalized as the ratio of the primary excitatory-to-inhibitory neurotransmitters, i.e. glutamate-to-GABA ratio [Liang et al., 2024, Lombardi et al., 2017, Baumgarten and Bornholdt, 2019, Bruining et al., 2020, Trakoshis et al., Gao et al., 2017]. It is thought that E/I controls criticality by modulating the brain's signal-to-noise ratio [Liang et al., 2024, Rubenstein and Merzenich, 2003].

Besides the implications to the critical brain hypothesis, understanding if E/I is related to HE may allow for easier estimation of excitatory and inhibitory neurotransmitters, as accurate E/I measurement is technically challenging [Ajram et al., 2019]. Magnetic resonance spectroscopy (MRS) is the only non-invasive method of measuring the ratio of glutamate (excitatory) to GABA (inhibitory) *in vivo* [Stanley and Raz, 2018]. Unfortunately, it has both limited spatial and temporal resolution [Gao et al., 2017, Ajram et al., 2019, Stanley and Raz, 2018]. Consequently, if HE could serve as a proxy for E/I, it would be much easier to estimate E/I in conditions of interest such as autism, Alzheimer's, and schizophrenia.

There are a handful of studies suggesting a link between HE and E/I, however they are all either computational models or animal studies [Liang et al., 2024, Poil et al., 2012, Lombardi et al., 2017, Baumgarten and Bornholdt, 2019, Bruining et al., 2020, Trakoshis et al., Gao et al., 2017]. Moreover, their findings are inconsistent, with some reporting positive linear, negative linear, or U-shaped relationships between the two variables (see Table 1). Thus, there is a need for further study, both to clarify the nature of a potential E/I-Hurst relationship, and also to confirm if this relationship indeed exists in the human brain. Therefore, the current study seeks to investigate the potential E/I-Hurst relationship in vivo, within the visual cortex during movie-watching and rest.

Table 1. Summary of Methods for Existing E/I-Hurst Studies

Citation	Study Type	HE Data Type	HE Calculation Method	E/I Type	E/I-Hurst Relationship
Poil et al. (2012)Poil et al. [2012]	Computational with in-house simulated model	Neuronal avalanche size	Detrendend fluctuation analysis (DFA)	Structural: number of E-to-I neurons	Inverse U

Citation	Study Type	HE Data Type	HE Calculation Method	E/I Type	E/I-Hurst Relationship
Bruining et al. (2020)Bruining et al. [2020]	Computational with model by Poil et al. (2012); modified in-house	Neuronal oscillation amplitude	DFA	Structural: number of E-to-I synapses	Inverse U
Gao et al. (2017)Gao et al. [2017]	Computational in vivo in rats and macaques	Local field potential (LFP)	PSD	Estimated from LFP	Positive linear
Lombardi et al. (2017)Lombardi et al. [2017]	Computational with in-house model	Neuronal avalanche size	PSD	Structural: number of E-to-I neurons	Negative linear
Trakoshis et al. (2020)Trakoshis et al.	Computational with simulated data; in vivo in mice	fMRI BOLD signal	Wavelet-based maximum likelihood method	E-to-I synaptic conductance	Positive linear

Methods

Study Participants

Ethics approval was granted by the Clinical Research Ethics Board at the University of British Columbia and BC Children's & Women's Hospital (H21-02686). Written informed consent was obtained from all participants. Twenty-six participants were scanned between the ages of 21 and 53.4.

After our analysis and performing quality assurance (see below), seven participants were removed for having poor quality data, leaving nineteen final participants, between the ages of 21.3 and 53.4 (mean ± sd: 30.1 ± 8.7 years; 9 males).

References

Laura A. Ajram, Andreia C. Pereira, Alice M. S. Durieux, Hester E. Velthius, Marija M. Petrinovic, and Grainne M. McAlonan. The contribution of [1H] magnetic resonance spectroscopy to the study of excitation-inhibition in autism. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, 89:236–244, March 2019. ISSN 0278-5846. doi: 10.1016/j.pnpbp.2018.09.010.

Michel Baranger. Chaos, Complexity, and Entropy: A physics talk for non-physicists. *New England Complex Systems Institute*, April 2000.

Danielle S. Bassett and Michael S. Gazzaniga. Understanding complexity in the human brain. *Trends in cognitive sciences*, 15(5):200–209, May 2011. ISSN 1364-6613. doi: 10.1016/j.tics.2011.03.006.

Lorenz Baumgarten and Stefan Bornholdt. Critical excitation-inhibition balance in dense neural networks. *Physical Review E*, 100(1):010301, July 2019. doi: 10.1103/PhysRevE.100.010301.

John Beggs and Nicholas Timme. Being Critical of Criticality in the Brain. *Frontiers in Physiology*, 3, 2012. ISSN 1664-042X.

Hilgo Bruining, Richard Hardstone, Erika L. Juarez-Martinez, Jan Sprengers, Arthur-Ervin Avramiea, Sonja Simpraga, Simon J. Houtman, Simon-Shlomo Poil, Eva Dallares, Satu Palva, Bob Oranje, J. Matias Palva, Huibert D. Mansvelder, and Klaus Linkenkaer-Hansen. Measurement of excitation-inhibition ratio in autism spectrum disorder using critical brain dynamics. *Scientific Reports*, 10(1):9195, June 2020. ISSN 2045-2322. doi: 10.1038/s41598-020-65500-4.

Olivia Lauren Campbell and Alexander Mark Weber. Monofractal analysis of functional magnetic resonance imaging: An introductory review. *Human Brain Mapping*, 43(8):2693–2706, March 2022. ISSN 1065-9471. doi: 10.1002/hbm.25801.

Gustavo Deco, Viktor K. Jirsa, and Anthony R. McIntosh. Resting brains never rest: Computational insights into potential cognitive architectures. *Trends in Neurosciences*, 36(5):268–274, May 2013. ISSN 0166-2236. doi: 10.1016/j.tins.2013.03.001.

Olga Dona, Geoffrey B. Hall, and Michael D. Noseworthy. Temporal fractal analysis of the rs-BOLD signal identifies brain abnormalities in autism spectrum disorder. *PLOS ONE*, 12(12):e0190081, December 2017a. ISSN 1932-6203. doi: 10.1371/journal.pone.0190081.

Olga Dona, Michael D. Noseworthy, Carol DeMatteo, and John F. Connolly. Fractal Analysis of Brain Blood Oxygenation Level Dependent (BOLD) Signals from Children with Mild Traumatic Brain Injury (mTBI). *PLOS ONE*, 12(1):e0169647, January 2017b. ISSN 1932-6203. doi: 10.1371/journal.pone.0169647.

Jianxin Dong, Bin Jing, Xiangyu Ma, Han Liu, Xiao Mo, and Haiyun Li. Hurst Exponent Analysis of Resting-State fMRI Signal Complexity across the Adult Lifespan. *Frontiers in Neuroscience*, 12, 2018. ISSN 1662-453X.

Richard Gao, Erik J. Peterson, and Bradley Voytek. Inferring synaptic excitation/inhibition balance from field potentials. *NeuroImage*, 158:70–78, September 2017. ISSN 1053-8119. doi: 10.1016/j.neuroimage.2017.06.078.

Bin Jing, Zhuqing Long, Han Liu, Huagang Yan, Jianxin Dong, Xiao Mo, Dan Li, Chunhong Liu, and Haiyun Li. Identifying current and remitted major depressive disorder with the Hurst exponent: A comparative study on two automated anatomical labeling atlases. *Oncotarget*, 8(52):90452–90464, August 2017. ISSN 1949-2553. doi: 10.18632/oncotarget.19860.

Meng-Chuan Lai, Michael V. Lombardo, Bhismadev Chakrabarti, Susan A. Sadek, Greg Pasco, Sally J. Wheelwright, Edward T. Bullmore, Simon Baron-Cohen, and John Suckling. A Shift to Randomness of Brain Oscillations in People with Autism. *Biological Psychiatry*, 68(12):1092–1099, December 2010. ISSN 0006-3223. doi: 10.1016/j.biopsych.2010.06.027.

Junhao Liang, Zhuda Yang, and Changsong Zhou. Excitation–Inhibition Balance, Neural Criticality, and Activities in Neuronal Circuits. *The Neuroscientist*, page 10738584231221766, January 2024. ISSN 1073-8584. doi: 10.1177/10738584231221766.

F. Lombardi, H. J. Herrmann, and L. de Arcangelis. Balance of excitation and inhibition determines 1/f power spectrum in neuronal networks. *Chaos: An Interdisciplinary Journal of Nonlinear Science*, 27(4):047402, March 2017. ISSN 1054-1500. doi: 10.1063/1.4979043.

Zhuqing Long, Bin Jing, Ru Guo, Bo Li, Feiyi Cui, Tingting Wang, and Hongwen Chen. A Brainnetome Atlas Based Mild Cognitive Impairment Identification Using Hurst Exponent. *Frontiers in Aging Neuroscience*, 10:103, April 2018. ISSN 1663-4365. doi: 10.3389/fnagi.2018.00103.

Voichiţa Maxim, Levent Şendur, Jalal Fadili, John Suckling, Rebecca Gould, Rob Howard, and Ed Bullmore. Fractional Gaussian noise, functional MRI and Alzheimer's disease. *NeuroImage*, 25(1):141–158, March 2005. ISSN 1053-8119. doi: 10.1016/j.neuroimage.2004.10.044.

S Ogawa, T M Lee, A R Kay, and D W Tank. Brain magnetic resonance imaging with contrast dependent on blood oxygenation. *Proceedings of the National Academy of Sciences*, 87(24):9868–9872, December 1990. doi: 10.1073/pnas.87.24.9868.

Seiji Ogawa and Tso-Ming Lee. Magnetic resonance imaging of blood vessels at high fields: In vivo and in vitro measurements and image simulation. *Magnetic Resonance in Medicine*, 16(1):9–18, 1990. ISSN 1522-2594. doi: 10.1002/mrm.1910160103.

Simon-Shlomo Poil, Richard Hardstone, Huibert D. Mansvelder, and Klaus Linkenkaer-Hansen. Critical-State Dynamics of Avalanches and Oscillations Jointly Emerge from Balanced Excitation/Inhibition in Neuronal Networks. *Journal of Neuroscience*, 32(29):9817–9823, July 2012. ISSN 0270-6474, 1529-2401. doi: 10.1523/JNEUROSCI.5990-11.2012.

J. L. R. Rubenstein and M. M. Merzenich. Model of autism: Increased ratio of excitation/inhibition in key neural systems. *Genes, brain, and behavior*, 2(5):255–267, October 2003. ISSN 1601-1848.

Mikail Rubinov, Olaf Sporns, Jean-Philippe Thivierge, and Michael Breakspear. Neurobiologically Realistic Determinants of Self-Organized Criticality in Networks of

Spiking Neurons. *PLOS Computational Biology*, 7(6):e1002038, June 2011. ISSN 1553-7358. doi: 10.1371/journal.pcbi.1002038.

Jeffrey A. Stanley and Naftali Raz. Functional Magnetic Resonance Spectroscopy: The "New" MRS for Cognitive Neuroscience and Psychiatry Research. *Frontiers in Psychiatry*, 9:76, March 2018. ISSN 1664-0640. doi: 10.3389/fpsyt.2018.00076.

Klaas Enno Stephan and Alard Roebroeck. A short history of causal modeling of fMRI data. *NeuroImage*, 62(2):856–863, August 2012. ISSN 1053-8119. doi: 10.1016/j.neuroimage.2012.01.034.

Yang Tian, Zeren Tan, Hedong Hou, Guoqi Li, Aohua Cheng, Yike Qiu, Kangyu Weng, Chun Chen, and Pei Sun. Theoretical foundations of studying criticality in the brain. *Network Neuroscience*, 6(4):1148–1185, October 2022. ISSN 2472-1751. doi: 10.1162/netn_a_00269.

Stavros Trakoshis, Pablo Martínez-Cañada, Federico Rocchi, Carola Canella, Wonsang You, Bhismadev Chakrabarti, Amber NV Ruigrok, Edward T Bullmore, John Suckling, Marija Markicevic, Valerio Zerbi, Simon Baron-Cohen, Alessandro Gozzi, Meng-Chuan Lai, Stefano Panzeri, and Michael V Lombardo. Intrinsic excitation-inhibition imbalance affects medial prefrontal cortex differently in autistic men versus women. *eLife*, 9:e55684. ISSN 2050-084X. doi: 10.7554/eLife.55684.

Maobin Wei, Jiaolong Qin, Rui Yan, Haoran Li, Zhijian Yao, and Qing Lu. Identifying major depressive disorder using Hurst exponent of resting-state brain networks. *Psychiatry Research: Neuroimaging*, 214(3):306–312, December 2013. ISSN 0925-4927. doi: 10.1016/j.pscychresns.2013.09.008.

Alle Meije Wink, Frédéric Bernard, Raymond Salvador, Ed Bullmore, and John Suckling. Age and cholinergic effects on hemodynamics and functional coherence of human hippocampus. *Neurobiology of Aging*, 27(10):1395–1404, October 2006. ISSN 0197-4580. doi: 10.1016/j.neurobiolaging.2005.08.011.

Vincent Zimmern. Why Brain Criticality Is Clinically Relevant: A Scoping Review. *Frontiers in Neural Circuits*, 14, 2020. ISSN 1662-5110.