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

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