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BOLD or Just Bold: Analyzing the tradeoffs of the fMRI's Signature Contrast Technique Compared to the Traditional Structural MRI

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Abstract: ***Functional magnetic resonance imaging has tipped the scales of neuroscience in its favor by allowing the noninvasive imaging of brain activity due to the blood-oxygen-level-dependent contrast. Despite this, BOLD fMRI remains limited due to its dependence on localized vascular activity in the brain rather than direct measures of neuronal activity. This introduces ambiguities in the interpretations of these signals. This study aims to investigate the tradeoffs between MRI and BOLD fMRI. Drawing on several peer-reviewed studies, this synthesis presents the current knowledge on contrast physics, the biological foundations of the BOLD signal, and its confounds. This paper also aims to reveal the limitations of BOLD, along with certain misapprehensions regarding the accuracy of its interpretations, and issues related to the variability of its signal, clinical translatability, and calibration techniques.***

To address the problems presented in BOLD's signal validity, this paper proposes a new framework, Adaptive Vascular Calibration, which combines the technique of breath-hold cerebrovascular reactivity mapping with region-specific hemodynamic lag estimations to provide a solution for inter-individual variability and voxel-wise vascular variability (differences in vascular responsiveness across individual voxels in an MRI scan, which can cause variations in BOLD signal strength and timing) in BOLD responses. AVC differs from previous models in its aim to integrate vascular fingerprinting directly into preprocessing pipelines for both task-based and resting-state fMRI, which should enable individual-focused and physiologically accurate interpretations of signals. This proposal also represents a crucial step toward harmonizing BOLD's complexity with the precision required in clinical settings and research.

Keywords: BOLD contrast, fMRI, MRI, neuroimaging, hemodynamic response

I. INTRODUCTION

Magnetic Resonance Imaging (MRI) is an important tool that has become a keystone in biomedical research and clinical diagnostics due to its unique ability of capturing detailed images of the body without requiring ionizing radiation or being an invasive procedure, which also makes it safer for patients[1]. Ever since they were developed in the 1970s, MRIs have undergone significant metamorphosis, all thanks to innovations in several

different facets of MRI technology: coil design, pulse sequences, magnetic field strength, and more. Such developments have enabled much more detailed visualizations of soft tissues[23].

One of the most significant advancements in MRI technology has been the development of the fMRI or the functional MRI. The fMRI uses a method known as Blood-Oxygen Level Dependent (BOLD) contrast, which has allowed researches to study activity in the brain by monitoring changes in the levels of blood oxygen in specific areas of the brain through a change in blood flow that occurs in response to increases or decreases in local metabolic demands, especially due to increased neuronal activity in the brain. This scientific term for this response is the Hemodynamic Response[4].

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BOLD fMRI is dissimilar to the traditional structural MRI due to its emphasis on several dynamic physiological changes instead of static tissue properties, like tissue density. In other words, the BOLD fMRI captures how neurons that are active promote increased blood flow in their vicinity, which therefore changes the levels of deoxyhemoglobin, which is hemoglobin that does not contain Oxygen. Since deoxyhemoglobin in paramagnetic, which means that it is experiences a weak attraction by a magnet's poles, but it does not retain any permanent magnetism, its presence influences the decay of the T_2* signal, which is fundamental to how BOLD imaging functions[5]. But this comes with a significant limitation: BOLD fMRI measures vascular responses other than directly measuring neuronal activity, which may lead to misinterpretations of the results obtained from it[6].

Over the past three decades, BOLD fMRIs have been in use across several fields of study: cognitive neuroscience, psychiatry, surgical planning, and the analysis of resting-state networks in the brain, all of which speak of its significance in both medicine and research[7]. However, its quick rise in popularity, more often than not, surpasses our understanding of its underlying processes and functionalities. Misunderstandings with regards to the specificity and reliability of BOLD signals are still prevalent, especially when they are taken to be direct measurements of activity within the brain. Plus, issues such as BOLD's highly imperfect spatial and temporal resolution, its high susceptibility to noise and artefacts, and its immense reliance on healthy blood vessels in the brain raise questions about its validity in both clinical contexts and scientific research[8].

The aim of this paper is to explore these complexities through a detailed comparative analysis presented in the form of a literature review. It will explore how MRI technology has evolved from structural MRI to functional MRI, elaborate on their own respective physiological and biological bases, and evaluate the strengths and weaknesses of each of them. In doing so, this work seeks to provide a clearer understanding of the trade-offs involved with BOLD fMRI. Alongside this, this body of work hopes to foster more educated and informed interpretations of BOLD fMRI, promote its responsible use, and encourage further advancements in the use of the fMRI as an invaluable instrument for both research purposes and clinical practices.

II. LITERATURE REVIEW

A. *Evolution: From Structural MRI to Functional MRI*

1) *Historical Foundations of MRI*

The evolution of MRI technology is rooted in decades of heavy, interdisciplinary work based on NMR (Nuclear Magnetic Resonance) principles. Taking ideas from the development of NMR by Bloch and Purcell in the 1950s and the concept of the spin-echo by Hahn, Raymond Damadian, in 1976, recognized that malignant tissue exhibited distinct T_1 and T_2 relaxation signatures. T_1 and T_2 relaxation signatures are responsible for describing how quickly H^+ ions, also known as protons, return to their normal state after a radiofrequency (RF) pulse in the MRI. T_1 measures recovery along the magnetic field of the MRI, while T_2 measures the decay along the same. This finding demonstrated the MRI's diagnostic potential[9].

This metamorphosis occurred in the 1970s, when Paul Lauterbur introduced spatial encoding via magnetic field gradients, which assigns locations to signals by varying the magnetic field across the body and causing position-dependent changes in resonance frequency, and Peter Mansfield pioneered echo-planar imaging (EPI), thus allowing the real-time scanning of anatomical structures and laying the foundation for high-speed image acquisition[10]. This era led to the adoption of MRI in clinics by the 1980s, which bolstered the role of structural MRI in medical diagnostics and fetched Lauterbur and Mansfield the Nobel Prize in Medicine in 2003[11].

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2) Emergence of Functional Imaging Principles

Although early MRI techniques focused primarily on anatomical contrast, the theoretical concept stating that neural activity has an influence on localized cerebral blood flow is rooted in 19th-century physiology, more specifically, in Angelo Mosso's experiments demonstrating increasing cranial pulsation during tasks aimed at cognition in the late 1800s[12]. Although it is elementary, this work laid a base for later imaging. In the late 1980s, Michael Moseley and colleagues at Stanford University began pioneering research on diffusion imaging, an MRI-based technique that measures the random motion of water molecules within tissues. Because water molecules move differently in healthy versus damaged or structured tissue, this approach provided a new way to probe the microstructure of the brain. Around the same time, Denis Le Bihan and others developed Diffusion Tensor Imaging (DTI). DTI is a more advanced form of diffusion imaging that tracks the directional movement of water molecules. Since water tends to diffuse along the length of nerve fibers rather than across them, DTI can map the orientation and connectivity of white matter tracts in the brain. Together, these advances opened the door to physiology-based neuroimaging, demonstrating that the movement of water, and indirectly blood flow, could be mapped non-invasively to reveal structural and functional information about the brain[13].

3) Landmark Discovery of BOLD Contrast

The turning point to functional MRI was in 1990 with Seiji Ogawa and colleagues showing how deoxyhemoglobin's paramagnetic properties generate detectable T_2*-weighted signal changes that respond to local oxygenation shifts in blood in rodent brain tissue[14]. Through monitoring inhaled oxygen levels, Ogawa and team correlated these changes to differences in magnetic susceptibility, creating the physiological basis for BOLD contrast[15].

4) First Human Functional MRI Studies

The first examples of human fMRI studies came up quickly in 1991. At the San Francisco meeting of the Society for Magnetic Resonance in Medicine (SMRM), two independent groups, Massachusetts General Hospital (MGH) and the University of Minnesota, presented these findings:

- Jack Belliveau and colleagues mapped changes in cerebral blood volume (CBV) during stimulation through visual means, using EPI sequences, which are echo-planar imaging sequences that rapidly acquire whole MR images after one single excitation by collecting several echoes, and gadolinium-based agents, creating the world's first MRI-based functional maps in human beings[16].
- Kenneth Kwong and colleagues used gradient-echo EPI to demonstrate endogenous BOLD-based imaging. Their movie of visual cortex activation surprised the community of neuroscience and started a large pursuit of BOLD fMRI[17].

5) Early Human fMRI Publications

In 1992, the findings from the San Francisco presentations were consolidated in peer-reviewed publications. Kenneth Kwong and colleagues published their work in PNAS, documenting dynamic brain activation during visual stimulation, while Bandettini and colleagues at the Medical College of Wisconsin reported motor cortex activation during a finger-tapping task in Magnetic Resonance in Medicine. Around the same time, Seiji Ogawa's group at the University of Minnesota confirmed that deoxyhemoglobin was the endogenous source of contrast, firmly establishing the physiological basis of BOLD fMRI. Additional groups at Yale, Göttingen, and the NIH soon replicated these results, which helped solidify the doability and reproducibility of the method[18].

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6) Technological Evolution: Field Strength and Sequence Advances

Despite this rapid progress, early BOLD studies faced significant technical limitations. Most were conducted on 1.5 Tesla scanners, which, while standard for clinical imaging, provided relatively low signal-to-noise ratio and limited spatial resolution for functional studies. These constraints reduced sensitivity to the small susceptibility changes underlying BOLD contrast[19].

- The transition to 3T systems in the following years provided a substantial improvement, offering higher SNR, greater contrast sensitivity, and enhanced spatial resolution, which in turn made functional imaging more robust and reliable.
- SNR, contrast sensitivity, and temporal resolution has been enhanced by 3T scanners. This is because 3T MRI scanners improve imaging by leveraging the higher magnetic field strength that they have. This increased field has double the net magnetization that 1.5T scanners have, which leads to a significantly high SNR, improving image quality and clarity. The increased SNR also enables the use of faster imaging sequences without compromising upon the resolution, allowing for the better capture of dynamic processes and improving temporal resolution. Plus, the stronger field improves differences between T1 relaxations in different tissues, increasing its sensitivity to contrast and making subtle anatomical or pathological differences more visible to the human eye20.
- Along the same lines, 7T imaging introduced further gains in the sensitivity and spatial specificity of MRIs, although it has done so with increased susceptibility to artefacts and great concerns with regards to safety due to its ultra-high magnetic field[21].

B. Physics of Contrast Mechanisms: T_1, T_2, and T_2 (BOLD)*

1) T_1 and T_2 Relaxation: The Basis of Structural MRI

T_1 relaxation is the process where protons realign back to the static magnetic field (B_0) after excitation. A "short T_1" means the protons realign quickly, so these tissues recover their longitudinal magnetization faster and appear bright on T_1-weighted images. Fat, for example, has a short T_1 and therefore looks bright. On the other hand, a "long T_1" means slower recovery, so tissues such as cerebrospinal fluid are darker on T_1-weighted scans. Because T_1 contrast highlights differences in recovery speed, it provides excellent anatomical detail. When gadolinium contrast is administered, it shortens the T_1 of nearby tissues, making vascular structures or pathological regions (such as tumors or sites of breakdown in the blood–brain barrier) appear brighter and more conspicuous against normal tissue[22].

T_2 relaxation refers to how quickly protons lose phase coherence in the transverse plane after being excited by a radiofrequency pulse. A "long T_2" means that the signal from those tissues decays more slowly, so they look bright on T_2-weighted images, while a "short T_2" means faster signal decay and darker look. Cerebrospinal fluid, for example, has a long T_2 and therefore appears bright, while fat and white matter have shorter T_2 values and appear darker. This contrast is clinically useful because many pathological processes, like edema, lesions, and inflammation, increase the water content of tissues. Extra water lengthens the T_2 relaxation time, making these abnormalities stand out as bright regions against the darker background of surrounding fat and white matter[23].

By controlling repetition time (TR) and echo time (TE) carefully, MRI sequences preferentially enhance T_1 or T_2 effects, creating the conventional contrast employed in clinical imaging[24].

2) T_2: Effective Transverse Relaxation and BOLD Imaging*

T_2* quantifies the observed transverse decay, accounting not only for intrinsic molecular interactions (T_2) but also additional dephasing because of magnetic field inhomogeneities, i.e, how quickly the MRI signal dephases because of tiny variations or imperfections in the magnetic field across the tissue. The relationship is:

$$\frac{1}{T_2^*} = \frac{1}{T_2} + \frac{1}{T_{inhom}}$$

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Here, T_{inhom} arises from spatial variations in B_0 - the main static magnetic field in the MRI, susceptibility differences between tissues, and gradients across voxel boundaries. T_2* is always shorter than (or equal to) T_2[25].

Gradient-echo (GRE) sequences are MRI sequences that generate signals using gradient reversals instead of 180° refocusing pulses. This approach makes them sensitive to both spin-spin interactions and magnetic field inhomogeneities, producing T_2*-weighted images. Such images are particularly useful for detecting hemorrhage, iron deposition, and other sources of magnetic susceptibility, and they form the basis of BOLD fMRI, where deoxyhemoglobin serves as the intrinsic source of contrast[2627].

*3) BOLD Contrast Mechanism: Linking Hemodynamics to T_2**

The Blood-Oxygen-Level Dependent (BOLD) effect is dependent upon the paramagnetic effect of deoxyhemoglobin. With neural tissue activation, there is greater blood flow (neurovascular coupling), and local deoxyhemoglobin levels decrease, i.e., there is reduced magnetic field distortion and hence longer T_2* relaxation times and an increase in T_2*weighted GRE sequence signal. Areas with higher oxyhemoglobin concentration hence get brighter compared to baseline[28].

T_2 and T_2* effects both make contributions to BOLD contrast within 1.5–3 T, but at ≥7 T, diffusion and microscopic inhomogeneities are dominant, and susceptibility sensitivity rises with field strength, making BOLD detection of microvasculature signals easier[29].

GRE sequences with an echo time close to tissue T_2* (~30-50 ms) maximize BOLD sensitivity, as they allow signal differences driven by deoxyhemoglobin to completely manifest. Spin-echo sequences can improve spatial specificity by reducing contributions from large vessels, even though this comes at the expense of overall signal intensity. In both cases, the MRI system is responsible for detecting the resulting variations in signal phase and amplitude through receiver coils, and these measurements are reconstructed into images that reflect differences in T_2* contrast across brain tissue[30].

4) Comparative Overview[31]

Mechanism	Physical Basis	Imaging Use	Strengths	Limitations
T_1-Weighted	Longitudinal magnetization recovery	Anatomical Imaging, Contrast-enhanced scans	Excellent Tissue Differentiation	Limited Sensitivity to fluid, pathology
T_2-Weighted	Intrinsic spin-spin coherence decay	Edema, inflammation, lesion detection	Sensitive to fluid-rich pathological states	Lower anatomical detail compared to T_1
T_2-Weighted*	T_2 + Magnetic susceptibility, inhomogeneity	Functional imaging via BOLD, susceptibility imaging	Detects deoxyhemoglobin changes, sensitive	Prone to distortion, large-vessel artefacts

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5) Implications for fMRI Tradeoffs

- Indirectness: BOLD is an indirect measure of neural activity. It measures vascular/metabolic responses rather than neuronal spikes[32].
- Spatial specificity: GRE-BOLD tends to be biased toward localizing near large draining veins, but spin-echo or high-field acquisition can mitigate such bias at the cost of SNR loss33.
- Temporal tradeoff: Onset of BOLD response is several seconds after neural activation and limits temporal resolution compared to electrophysiological techniques34.
- Field dependency: Larger magnetic fields enhance susceptibility sensitivity but compromise artifacts and SAR limits (Specific absorption rate, a safety measure of RF energy deposition in tissue), which refer to the maximum amount of radiofrequency energy that can be absorbed by the body, measured in watts per kilogram, to ensure safety during exposure to RF fields[35].

C. Biological Basis and Hemodynamic Response

1) Neurovascular Coupling: Cellular and Network Mechanisms

Neurovascular coupling or NVC refers to the physiological mechanism by which neural activity boosts local cerebral blood flow (CBF) to correspond to the metabolic need[36].

Key Cellular Players:

- Neurons: Begin by releasing neurotransmitters (such as glutamate).
- Astrocytes: Stimulated by glutamate, elevate intracellular calcium, and secrete vasodilators (e.g., nitric oxide, VIP).
- Pericytes: Contractile cells of capillaries; their in-vivo function in the dilation of vessels remains controversial.
- Interneurons: Release vasoactive substances (NO, neuropeptide Y), further modulating microvascular response.

The neurovascular unit functions as an integrated unit, with multiple cell types being involved in the regulation of local blood supply.[37]

2) The Hemodynamic Response Function (HRF)

Sequence of Events:

- First Dip (~1–2 s): Transient reduction in BOLD signal when oxygen is utilized.
- Principal Rise and Peak (~4–6 s): Blood flow augmentation surpasses metabolic demand, and BOLD signal is at its peak.
- Post-Stimulus Undershoot (~10–16 s): Signal drops below baseline, perhaps secondary to prolonged vascular compliance or continued metabolic requirements.
- Length: The physiological hemodynamic reaction takes approximately 10 seconds.
- Implications for Imaging: Standard fMRI sampling rates (TR 1–3 s) typically have enough resolution to capture HRF shape, but fast or overlapping events necessitate sophisticated design and modeling.[38]

3) Modeling Approaches and Nonlinearity

Canonical Modeling: Most analyses use a standard "canonical" HRF, a gamma function, convolved with task timing.[39]

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Basis Sets: Linear basis sets (e.g., FLOBS) enable the model to fit flexibly HRF timing, amplitude, and dispersion across individuals or populations.[39]
Nonlinearities:[40]
Repeated or sustained stimuli result in:

- ~15–20% attenuation in amplitude
- Delayed peak (+10–12%)
- Wider response (6–-14%)
- They are vascular, and not neural, nonlinearities.

4) Inter-Individual and Population Variability

- Age and Disease: Aging slows down HRF rise time, reduces peak, and slows down recovery. Stroke, diabetes mellitus, and neuropsychiatric illnesses (e.g., depression) alter neurovascular dynamics, complicating interpretation.[41]
- Genetic and Metabolic Factors: Genetic polymorphisms, caffeine consumption, and lipid levels can alter BOLD signal timing and amplitude, unrelated to neural activity.[42]

5) Importance for fMRI Design and Interpretation

- Temporal Constraints: Slow HRF constrains temporal resolution. Block designs increase power for sustained activity, whereas event-related designs include jittering and deconvolution to isolate overlapping responses.[43]
- Physiological and Technical Noise: Cardiovascular and respiratory cycles, motion, and systemic vascular oscillations can contaminate signals. Appropriate modeling and preprocessing are required to remove true brain activity. Summary: Precise interpretation of BOLD-fMRI requires taking into account technical limits as well as biological variability. Researchers need to account for these at the study design and data analysis level.[44]

D. Misconceptions: BOLD as a Direct Neuronal Proxy

The widespread and overly simplified view of the BOLD signal is that greater BOLD amplitude simply equals greater neuronal firing. But a large body of empirical evidence contradicts this: BOLD reflects neurovascular dynamics, not electrical activity per se.

1) Bold Correlates More Strongly with Synaptic Input (LFPs) Than Spike Rate

Landmark simultaneous recordings from primate visual cortex (Logothetis et al., 2001) showed that BOLD signal is more strongly correlated with local field potentials (LFPs), a surrogate for synaptic and integrative processing, than with multi-unit spiking activity (MUA). Spiking accounted for some variance, but LFPs accounted for changes in BOLD between recording locations[45].

2) Regional Variability with The Example of The Hippocampus

Additional research in human hippocampal regions showed that activity in the parahippocampal cortex (a region surrounding the hippocampus that helps with memory and spatial processing) measured by BOLD response (Blood-Oxygen-Level-Dependent signal, the main signal used in fMRI to track changes in blood flow linked to neural activity) was moderately correlated with theta-band LFPs (local field potentials, brain oscillations in the 4-8 Hz frequency range associated with memory, navigation, and

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cognitive control). Specifically, the correlation was $r^2 = 49$, meaning that about half of the variance in the fMRI signal could be explained by these rhythmic neural fluctuations.

However, this BOLD response was not correlated with spike rate (the firing rate of individual neurons, measured as action potentials per unit time) in the hippocampus proper (the CA1–CA3 subfields of the hippocampus).

This dissociation occurs because the hippocampus has a highly complex balance of excitatory neurons (which drive activity) and inhibitory interneurons (which suppress activity).

These interactions mean that synaptic inputs (electrical signals arriving from other brain regions, which strongly influence LFPs and thus BOLD) do not always lead to proportional spiking outputs (neuron firing). In other words, the hippocampus can show strong rhythmic input activity without a corresponding change in the number of neurons firing, which explains why BOLD aligns with oscillatory activity (LFPs) but not with raw spike counts.[46].

3) How Spatial Scale Matters

Comparative studies in the feline visual cortex (the part of a cat's brain that processes visual information) showed that the relationship between BOLD signals (Blood-Oxygen-Level-Dependent fMRI signals that reflect changes in blood flow and oxygenation) and neuronal activity (measured through electrical signals such as spiking or local field potentials) depends on spatial resolution.

At supramillimeter resolutions (spatial scales larger than 1 mm, for example 2–3 mm voxels in fMRI), the relationship is relatively linear, meaning that increases in neural activity produce proportional increases in the BOLD response.

However, at higher resolutions (closer to or below 1 mm, such as single-electrode recordings that capture very local neuronal activity), this relationship breaks down. At such fine scales, correlations between BOLD and neuronal measures become highly variable and inconsistent, so they cannot be used to reliably predict one from the other.

This suggests that BOLD signals are more stable and meaningful when averaged over larger populations of neurons, but at very fine-grained levels, local variations in blood flow and microcircuitry cause the coupling between fMRI signals and neuronal activity to become unreliable[47].

4) Resting State BOLD and Transient, High-Amplitude Neural Events

Increasing evidence indicates that resting-state BOLD networks can be an outcome of distinct, high-amplitude neural co-activation events, not of persistent low-amplitude oscillations. These events, observable from LFP recordings in animals, seem to be the substrates of the temporal dynamics that are usually analyzed in rs-fMRI studies[48].

5) Additional Vascular Misconceptions and Confounds

In addition to neuronal specificity concerns, BOLD is affected by vascular physiology: It presumes equal neurovascular coupling, but variables such as age, endothelial function, disease, and subject vascular reactivity affect hemodynamic responses in a non-predictable manner49.

Because the brain is never actually at rest, global baseline variability (the fluctuation in overall resting or background activity of a system that occurs independently of task-related changes) may reflect systemic or non-neuronal effects that will be eliminated by standard preprocessing, potentially discarding relevant network information50.

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6) Summary of Misconceptions[51]

Misconception	Clarification
BOLD equals neuronal firing	BOLD aligns better with synaptic input (LFP), not spiking output.
Uniform neurovascular coupling	Coupling varies by region, age, health, and anatomy.
Fine-scale spatial accuracy	Robust at millimeter scale, unreliable at sub-millimeter resolution.
Resting BOLD reflects ongoing activity	Driven by sporadic high-amplitude events, not continuous low-level oscillations.

7) Implications for Interpretation

Neuroscience experiments should regard BOLD activations as evidence of integrative neuronal input, not as separate output firing. Clinical use, particularly in vascular disease or elderly patients, should take into account changed hemodynamic responses when using BOLD as a surrogate marker[52].

Methodological triangulation, such as EEG/fMRI or calibrated CBF techniques, assists in resolving vascular vs. neuronal contributions and provides interpretative precision[53].

In short, interpreting BOLD as a direct neuronal surrogate is not scientific. Instead, BOLD may be interpreted as a vascularly mediated, integrative signal, one that is controlled by synaptic inputs and local circuitry, and varies by the vasculature. This is something we need to know before moving on to the next sections, comparing BOLD fMRI to anatomical MRI and delving into its functional translational application.

E. Strengths and Weaknesses of BOLD fMRI

1) Strengths of BOLD fMRI

a) Noninvasiveness and Wide Availability

BOLD fMRI takes advantage of endogenous contrast without radioactive tracers or invasive procedures and is therefore suitable for repeated use in research subjects and clinical populations. It is also widely available in both clinical and academic settings and can be used with high-resolution anatomical imaging in one session[54].

b) High Spatial Resolution

Typical voxel sizes are 2–3 mm, enabling millimeter-scale localization of activation, and in ultra-high field scanners (7 T) submillimeter resolution is achievable. This is superior to surface-biased modalities such as EEG/MEG or the comparatively poor resolution of PET, and thus BOLD fMRI is the modality of choice for mapping functional networks and precise cortical areas[55].

c) Whole-Brain Coverage

Relative to techniques restricted to cortical regions (e.g., surface EEG) or contrast agent-based (e.g., CBV-based perfusion scans), BOLD fMRI quantifies dynamic activity throughout the whole brain volume, making it possible to map in detail task-activated and resting-state networks[56].

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d) Empirical Power and Utility in Neuroscience

More than three decades of application have established optimized standardized acquisition protocols and analysis pipelines to support large-scale research in cognitive neuroscience, developmental neuroimaging, and clinical research. Its flexibility encompasses task-evoked tasks, resting-state connectivity, and network dynamics studies[57].

e) Complementarity with Other Modalities

BOLD fMRI is suitably complemented by EEG or MEG, which offers electrophysiological temporal resolution with high spatial resolution. It also complements perfusion methods such as arterial spin labeling (ASL, a preprocessing step in fMRI analysis where the average signal from the entire brain is removed from each voxel's time series, intended to reduce noise but sometimes introducing artificial anti-correlations) to provide calibrated, quantitative estimates of neurovascular response[58].

2) Weaknesses of BOLD fMRI

a) Poor Temporal Resolution

The BOLD response has a peak of about 5–6 seconds following neuronal activation, and therefore it is slow compared to millisecond-order neural function. This renders it impossible to resolve fast cognitive sequence or event-related response timing accuracy. Although jittered rapid event-related designs reduce this to some extent, they remain less accurate than EEG/MEG timing ability[59].

b) Susceptibility to Physiological and Motion Artifacts

BOLD signals are susceptible to head motion noise, respiration-induced fluctuations, and cardiac pulsatile motion, all of which can be temporally correlated with task performance and therefore taint activation maps. Small head motion (0.3–0.4 mm) can generate signals that can simulate neuronal activation, particularly at tissue-cerebrospinal fluid interfaces[60].

c) Spatial Specificity Limitations

Gradient-echo (GE) BOLD is vulnerable to signals from large draining veins and may mis-localize the true neural source. This can be minimized by using spin-echo or high-field imaging with the cost of decreased signal-to-noise ratio (SNR) and increased technical complexity[61].

d) Indirect Signal Sources

Pharmacologic agents (such as sedatives, caffeine), age, vascular disease, and metabolic disorders can change local flow and cerebral vascular reactivity and affect BOLD signal independently of the change in neurons. The BOLD signal reflects the combined effects of cerebral blood flow (CBF), cerebral blood volume (CBV), and the cerebral metabolic rate of oxygen consumption ($CMRO_2$). Each of these factors can influence the signal differently, sometimes in opposing ways, so changes in BOLD do not map directly onto neural activity but instead represent a balance of these interacting processes[62].

e) Statistical and Reproducibility Challenges

Parametric group-level inferences are vulnerable to erroneous assumptions regarding spatial autocorrelation. There has been evidence of increased cluster-level false positives (up to 60%) in SPM, FSL, and AFNI software during thresholding of uncorrected

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data. Preprocessing decisions, including smoothing, regression of physiological noise, or filtering of data, may affect functional connectivity measures and reproducibility[63].

f) Design Constraints and Interpretative Risks

Block designs are powerful statistically but rigid and subject to confounding bias from baseline drift and habituation. Event-related designs are more adaptable but less powerful with greater signal overlap, and therefore deconvolution is required[64]. Task-based fMRI is also often not possible in cognitively impaired patients or in children, leading to the need for resting-state methods, which then are plagued by non-standardization and interpretive uncertainty[65].

BOLD fMRI refers to the underlying technique that measures changes in MRI signal driven by differences in blood oxygenation. Both task-based fMRI and resting-state fMRI are applications of this method. In task-based fMRI, participants perform a specific activity, such as viewing images or pressing a button, and changes in the BOLD signal are analyzed to identify brain regions involved in that function. In resting-state fMRI, participants remain at rest, and researchers study spontaneous BOLD fluctuations to examine how different brain regions are functionally connected. Thus, task-based and resting-state fMRI differ in experimental design, but both rely on BOLD contrast as the source of signal[66].

F. Common Themes and Technical Debates in BOLD fMRI

1) Neurovascular Uncoupling: A Critical Controversy

One of the main debates is whether BOLD signal always an accurate reflection of neural activity in all conditions. Although BOLD is an outcome of neurovascular coupling, coupling neuronal energy demand and hemodynamic responses, it may deviate at times due to modulatory signals or pathological states. Sirotin and Das (2009) observed hemodynamic cycles in animal visual cortex in the absence of concurrent neural activity, indicating neuromodulatory or anticipatory vascular control mechanisms. Critics say that even such deviations remain neurogenic in character, but the findings point out that BOLD cannot always be presumed to be purely due to neuronal input[6768].

Other diseases such as stroke, tumor, or aging may disrupt vascular reactivity and change coupling dynamics, producing mislocalized or reduced BOLD responses in pathological groups[69].

2) The Rise of Multi-Echo Planar Imaging (ME-EPI)

Improvements in acquisition technique like multi-echo (ME) echo-planar imaging (EPI) have generated controversy regarding tradeoffs in temporal penalty against spatial resolution. ME-EPI captures many echoes per excitation pulse, sampling across a range of echo times every voxel to optimize T_2* weighting and minimize susceptibility dropout in areas like the basal ganglia and inferior temporal cortex[70].

Advocates highlight ME-EPI's increased tSNR, higher CNR (contrast-to-noise ratio, a measure of how well a structure or signal stands out relative to background noise in an image; higher CNR means better visibility of features), and improved uniformity in regions prone to signal loss. Such losses often occur in areas with high iron content, since iron distorts the local magnetic field and

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accelerates T_2* decay, leading to reduced signal. These advantages are especially evident at ultra-high field strengths (7 T) with multi-slice simultaneous acquisition[71].

Increased TR and reduced slice coverage are called detriments by critics, necessitating higher acceleration and more sophisticated denoising algorithms such as ME-ICA[72].

3) Physiological Noise and Resting-State Confounds

Resting-state fMRI is highly vulnerable to physiological artifacts - respiration, cardiac pulsatility, and subject movement - that can saturate observed functional networks. Methods like global signal regression (GSR, a preprocessing step in fMRI analysis where the average signal from the entire brain is removed from each voxel's time series, intended to reduce noise but sometimes introducing artificial anti-correlations) have turned controversial; some consider GSR as necessary to minimize artifact, while others lament that GSR instills artificial anti-correlations between networks (e.g., DMN and task-positive networks)[73].

Other techniques involve regression of CSF and white matter signals, based on external recordings of physiology, or performing independent component analysis (ICA, a computational method used to separate a mixed fMRI signal into statistically independent components, often used to identify and remove artifacts) for the removal of neural signals from physiological noise[74].

4) Statistical Validity and Reproducibility Issues

Parametric statistical analyses commonly applied in BOLD fMRI (through SPM, FSL, AFNI) are based on spatial autocorrelation assumptions that might not be valid. Eklund et al. showed that parametric cluster-wise tests at common thresholding levels can produce up to 60% false-positive rates, a severe reproducibility problem.

Non-parametric permutation-based inference has more stringent control but is applied less often. Therefore, results based on cluster thresholding must be cautiously taken into account[7576].

5) Alternative and Emerging Contrast Methods other than BOLD in fMRI

Along with conventional T_2*-sensitive BOLD, fMRI is evolving with new contrast and acquisition techniques:

- Vascular Space Occupancy (VASO) imaging is an fMRI technique that differs fundamentally from BOLD. Instead of relying on the magnetic properties of hemoglobin, VASO directly measures changes in cerebral blood volume (CBV) by nulling the blood signal through a T_1 inversion pulse. This approach improves spatial specificity and reduces contamination from draining veins compared to BOLD, although it comes at the cost of lower sensitivity and more complex acquisition methods[77].
- Intravoxel Incoherent Motion (IVIM, an MRI technique that uses diffusion-weighted imaging to separate signals from molecular diffusion and microcirculatory blood flow, allowing capillary-level perfusion mapping) adds diffusion-weighted gradients to eliminate large-vessel signals and isolate perfusion signals at capillary level, potentially enhancing spatial resolution in activation mapping[78].
- Balanced SSFPs are also under consideration for fMRI based on their excellent SNR efficiency and lower distortion, but they are difficult with banding artifacts and complicated contrast dependencies[79].

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6) Implications for BOLD Trade-Offs

Together, these themes illustrate the field's effort to reconcile sensitivity, specificity, and validity for BOLD fMRI:

- Technical advances (such as ME-EPI) advance spatial reliability, becoming more sophisticated.
- Physiological variability requires intense preprocessing and multimodal design.
- Statistical validity issues need more robust structures of inference.

Other imaging contrasts provide complementary advantages, though with new constraints. Awareness of these controversies guides methodological design decisions, positions BOLD performance limitations, and directs future directions for functional imaging that seek to balance anatomical accuracy, physiological interpretability, and clinical utility.

G. Clinical Uses and Research Impact

1) Clinical Applications of BOLD fMRI

a) Presurgical Localization

BOLD fMRI is currently an important preoperative planning tool, especially for eloquent cortex mapping to prevent postoperative deficits. Experiments revealed that BOLD activation maps of primary language and motor areas can confidently inform surgical resection margins with high sensitivity and specificity, especially when used in conjunction with task paradigms matched to patient ability (e.g., finger tapping, verb generation). Clinical utility is enhanced when structural MRI is unavailable for contrast-based delineation of such functional areas[80].

b) Evaluation of Neurovascular Pathology

BOLD fMRI enables cerebrovascular reactivity (CVR) quantification in stroke, carotid stenosis, or cerebrovascular disease. BOLD response to hypercapnia (a condition of elevated carbon dioxide levels in the blood, often induced experimentally in fMRI to test cerebrovascular reactivity) with controlled levels by breath-holding or CO_2-inhalation tasks can predict areas at risk of ischemia and indicate vascular reserve. Decreased CVR in such paradigms is highly associated with impaired autoregulation and stroke risk[81].

c) Neuropharmacological Monitoring

While less common in clinical diagnostic practice, BOLD fMRI is used in research to quantify drug action, e.g., alteration of amygdala response following antidepressant treatment or modulation of reward circuitry with addiction research. Such quantifications enlighten drug mechanisms and efficacy, providing an unobtrusive biomarker for treatment-induced functional brain change[82].

d) Limitations in Widespread Clinical Use

Despite its research value, BOLD fMRI's broader clinical application faces several hurdles:

- Poor standardized task paradigms for a wide range of patient conditions.
- Variability of hemodynamic response by age, medication, or cerebrovascular health
- Limited insurance reimbursement and lack of regulatory approval for most clinical uses, particularly in neurology and psychiatry beyond presurgical mapping.

These limitations have kept BOLD fMRI from being used in routine clinical applications outside special centers[83].

2) Impact on Neuroscience Research

a) Spread of Functional Mapping

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Starting from the 1990s, BOLD fMRI has incited more than two decades of research in functional neuroimaging. Task-based activation has been used in a lot of studies to localize cognitive functions: language, attention, memory, emotion, and influenced models of brain organization (e.g., the default mode network, salience networks)[84].

b) Resting-State Functional Connectivity

One of the paradigmatic shifts enabled by BOLD fMRI was the discovery of coherent low-frequency oscillations during rest, defining intrinsic functional networks such as the default mode network (DMN, a network of brain regions that are active during rest and mind-wandering, and less active during task-focused behavior; includes the medial prefrontal cortex, posterior cingulate cortex, and angular gyrus), executive network, and sensorimotor systems. These findings have underpinned the growth of connectomics and network neuroscience, with applications in development, aging, brain disorder characterization, and individualized profiling[85].

c) Large Databases and Standardization

Studies like the Human Connectome Project (HCP), UK Biobank, and ABCD (Adolescent Brain Cognitive Development) have collected thousands of resting-state and task BOLD fMRI data. Such repositories enable cross-sectional and longitudinal analysis, reproducibility, and normative modeling, on which big-data methods to brain function and variability are built[8687].

d) Methodological Improvement and Biomarker Identification

The general availability of BOLD fMRI hastened methodological innovation, e.g., calibrated fMRI (a functional MRI method that combines BOLD imaging with a secondary measurement like an arterial spin labeling or hypercapnia challenge to quantitatively estimate brain oxygen metabolism and separate neural from vascular effects), high-field imaging, multi-echo EPI, and machine learning classifiers, to extract more valid, individualized, and biologically interpretable signals. These methods are intended to eliminate vascular from neuronal components and offer more reliable biomarkers for clinical translation (e.g., in Alzheimer's disease, depression, schizophrenia)[88].

3) Comparative Utility: BOLD fMRI versus Structural MRI[89]

Domain	Structural MRI	BOLD fMRI
Primary Use	Anatomical & lesion mapping	Functional activation & connectivity
Spatial Resolution	≤ 1 mm (high-resolution)	~2–3 mm, improved at high field
Temporal Resolution	Static	Seconds-scale HRF
Contrast Basis	Proton relaxation (T1/T2)	Hemodynamic changes (T_2*)
Clinical Standard	Core in clinical SARdiagnostics	Specialized applications (e.g., surgical mapping)
Research Power	Morphometry, volumetrics	Cognitive neuroscience, pharmacological studies

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Structural MRI is still the clinical gold standard for both the identification of pathology and for intervention guidance, while BOLD fMRI provides an additional view of function with interpretive subtlety and context-dependent validity[90].

4) Forward Outlook: Emerging Trends and Integration

- Calibrated fMRI: reconciling BOLD with CBF measurements (through ASL or hypercapnia calibration) to yield quantitative cerebral metabolic rate of oxygen consumption ($CMRO_2$) estimates and disentangling vascular from neural effects.[91]
- Pediatric and Geriatric Toolkits: paradigms that minimize cognitive load (e.g., passive observation, naturalistic stimulation) and physiological recording enable functional mapping in these populations92.
- Multimodal Integration: simultaneous EEG/fMRI, PET/fMRI integration, and high-density MEG co-registrations are improving spatiotemporal resolution and allowing biomarker development in psychiatric and neurological illness93.
- Standardization and Machine Learning: databases such as HCP have made normative modeling and machine learning classifiers possible to predict behavior, identify disease, and stratify treatment response.[94]

III. DISCUSSION

Functional magnetic resonance imaging (fMRI), in the guise of the blood-oxygen-level dependent (BOLD) contrast mechanism, has provoked a revolution in brain research. Scientists now can study the functioning brain with unmatched spatial resolution and noninvasive access. Nevertheless, despite its widespread application, the BOLD signal is intrinsically a secondary measure of neural function, subject not merely to subsequent neuronal events, but to intricate physiological and vascular processes. This discussion integrates the findings of the preceding sections, places the importance of BOLD fMRI in research and clinical application, and reveals a new methodological improvement designed to circumvent an enduring interpretive drawback of BOLD imaging.

BOLD fMRI has succeeded in mapping the functional anatomy of the human brain, from task-based localization of eloquent cortex to identification of intrinsic resting-state networks such as the default mode network, salience network, and executive control systems. Its noninvasiveness, coupled with the capacity to image whole-brain activity, has enabled applications in presurgical planning, neurological diagnosis, neuropsychological research, and cognitive neuroscience[95]. These strengths are counterbalanced by well-documented limitations. Most prominent among these is the fact that the BOLD signal is an index of changes in blood oxygenation, which are in turn modulated by both neuronal and non-neuronal factors. The spatial and temporal specificity of the BOLD signal is therefore limited, and its use as a surrogate for neuronal activity is conditional rather than absolute[96].

Multimodal neuroimaging strategies have been partial solutions to these constraints. Coupling BOLD fMRI with electroencephalography (EEG), magnetoencephalography (MEG), or arterial spin labeling (ASL) has allowed improved temporally more precise or physiologically more specific inferences about neural activity. Calibrated fMRI methods, which combine BOLD imaging with controlled hypercapnic stimulation or concurrent cerebral blood flow (CBF) measurement, have allowed cerebral metabolic rate of oxygen consumption ($CMRO_2$) to be estimated and thus separate vascular from metabolic effects.

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These advances notwithstanding, such calibrated or multimodal approaches are still largely the purview of research. Complexity, cost, and a lack of standardization preclude their general clinical use[9798].

In parallel, recent work has moved the analytic focus away from mean levels of activation and toward variability in the signal. Spatial and temporal fluctuations of resting-state BOLD signal, previously regarded as noise, are now valued to represent significant differences in brain structure and function[99]. Dynamic patterns have been associated with cognitive flexibility, disease, and developmental trajectories. Variability in itself is thus beginning to emerge as a potential useful biomarker that can be more sensitive and interpretable than static activation maps[100].

Amidst this advancement and restriction, there remains an underlying discrepancy: BOLD fMRI remains predicated on canonical models of the hemodynamic response function (HRF), even though inter-individual and regional heterogeneity of vascular dynamics has been well-documented. This discrepancy can potentially result in erroneous interpretation of activation maps, especially in clinical groups with compromised cerebrovascular physiology. Although data-driven HRF estimation and voxel-wise lag correction approaches have enhanced analytical precision, they remain disconnected from the individual's actual real-time state of physiology[101].

To fill this gap, I suggest a new method referred to as Adaptive Vascular Calibration, or AVC. This method integrates real-time physiological perturbation with subject-specific modeling of vascular dynamics to create region-specific vascular transfer functions[102]. The hypothesis is that every region of the brain possesses a unique response profile to vascular stimulation, characterized by local vessel structure, metabolic demand, and autoregulatory capacity. By transient cerebrovascular perturbation during scan acquisition - via mild, controlled stimuli such as breath-holding, hyperventilation, or low-level inhalation of carbon dioxide - one can cause a measurable difference in vascular tone. Simultaneous measurement of respiration, end-tidal CO_2 (the partial pressure or concentration of carbon dioxide measured at the end of an exhaled breath; used as a non-invasive indicator of arterial CO_2 levels and cerebrovascular reactivity), and blood pressure would yield a physiologically informative dataset.

The BOLD signals resulting from these perturbations would then be utilized to estimate transfer functions describing how each voxel transforms vascular input to BOLD signal output. These functions would include regional variations in response amplitude, latency, and duration[103]. Importantly, they would not just be employed to map cerebrovascular reactivity, as currently practiced, but to remap task-based or resting-state BOLD data recorded in subsequent sessions. In this manner, AVC would create a physiology-based correction layer (an additional data processing step in fMRI analysis that adjusts BOLD signals using measurements of the subject's physiological state - heart rate, blood pressure, CO_2 - to improve accuracy), enabling individualized interpretation of BOLD data in terms of each subject's own vascular profile[104].

Carefully reading the state of the art, I endorse the view that no available method exists that encompasses the full range of AVC methodology to the best of current literature. Certain techniques like breath-hold cerebrovascular reactivity mapping and dynamic HRF modeling have been employed in isolation. Some of them estimate voxel-wise vascular response delay or amplitude during hypercapnia tasks. Others employ machine learning models or Bayesian inference, which is a method of statistical inference in which Bayes' theorem is used to calculate the probability of a hypothesis, given prior evidence, to estimate HRFs from BOLD time series[105]. None of them, however, combine real-time physiological perturbation, individualized voxel-wise vascular transfer function (Mathematical models describing how each voxel in the brain transforms a vascular input into a measurable BOLD signal output)

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modeling, and downstream recalibration of functional imaging data into a unified analytical pipeline. AVC, therefore, is a true cutting-edge addition to functional neuroimaging[106].

Unlike multimodal approaches such as EEG-fMRI, which provide complementary information about neural timing, AVC directly improves the interpretability of the BOLD signal itself by calibrating out vascular confounds at the source. Physiological perturbation is not intended to enforce a uniform scale across subjects, but rather to reveal each individual's unique vascular response profile. The variability in amplitude, latency, and duration of responses across regions and individuals is precisely what AVC captures. These individualized transfer functions can then be used to correct subsequent BOLD measurements, transforming inter- and intra-subject variability from a source of error into a basis for more accurate interpretation.

The potential benefits of AVC are substantial. By correcting vascular variation in individual subjects, AVC may minimize false positives and negatives in fMRI analysis, especially in cerebrovascular disease patients, elderly with vascular changes due to aging, or with neuroinflammatory disease. In presurgical applications, AVC may enhance localization accuracy by correcting for regions of abnormal or deficient neurovascular coupling. In research applications, AVC may increase the sensitivity and specificity of activation detection and improve the interpretability of resting-state connectivity analysis. Moreover, AVC may be incorporated into real-time fMRI systems, facilitating adaptive task design and neurofeedback applications based on physiological state.

Of course, a number of issues need to be resolved before AVC can be achieved. Safety and tolerability of physiological perturbations need to be carefully controlled, especially in at-risk groups. Computational requirements for modeling and implementing voxel-wise transfer functions in real time require robust software tools. Standardization between sites would be necessary for reproducibility. But these issues are overcome with current technology. Physiological monitoring hardware is already commonplace in many MRI centers, and breath-hold or CO_2 inhalation tasks are well-validated. Real-time fMRI platforms and machine learning toolkits are becoming readily available[107].

In short, while BOLD fMRI has transformed functional brain mapping, it needs to mature now to overcome its very inherent deficiency: its basis on a generic, single model of vascular response. Adaptive Vascular Calibration provides a way to individualize and optimize fMRI analysis through its foundation in the vascular physiology of each subject. In the process, it repositions BOLD from a static surrogate to a calibrated, dynamic signal that more accurately mirrors the neural processes it aims to uncover. Such pursuit of so-called personalized neuroimaging is at once a technical imperative but also a conceptual transition toward an age when brain function is quantified not merely by location or timing but by physiological context, precision suited to the individual, and clinical utility.

IV. CONCLUSION

In brief, BOLD fMRI has revolutionized imaging and comprehension of the working human brain. Its emergence was a paradigm shift in the science of neuroscience, giving indirect access to the dynamic processes of neural systems underpinning cognition, behavior, and disease. And yet, despite all the revolutionary promise, BOLD is an inference technique: based upon the nuances of blood flow, oxygenation, and vascular physiology rather than direct measurement of neural activity. As the present paper has made evident, the virtues of BOLD imaging - spatial resolution, functional mapping properties, and accessibility - are inextricably bound up with its vices: compromised temporal accuracy, interindividual variability, and physiological ambiguity.

The BOLD fMRI and conventional structural MRI contrast illustrates an inherent compromise between anatomical resolution and functional insight. Structural MRI provides the physical map; BOLD fMRI tries to overlay that map with meaning. When the meaning is, however, tainted with neurovascular noise or oversimplified to a one-size-fits-all hemodynamic model, the scientific and clinical utility of BOLD fMRI is undermined.

This study has introduced a novel solution, Adaptive Vascular Calibration (AVC), to address this problem at its root. Through the use of real-time physiological perturbation modeling of the vascular response of individual subjects, AVC enables subject-specific calibration of the BOLD signal that respects the individual dynamics of every brain. We are aware of no other technique existing today that involves regional, voxel-level vascular calibration followed by resulting consequent functional imaging data recalibration. With this, AVC promises a future of neuroimaging that is more precise, more subject-specific, and more clinically significant.

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The future of fMRI is not a trade-off between structure and function, or between simplicity and complexity. It is embracing complexity in the service of clarity. It is putting physiology into every pixel of analysis. And it is recognizing that to understand the brain in the world, we don't just need to visualize its signals, we need to calibrate them to the person they are associated with.

On its journey to that future, what this paper does is twofold: a critical reconsideration of what has been accomplished, and a roadmap for innovation. It invites neuroscientists, clinicians, and engineers to think about what BOLD fMRI could be: not simply an activation map, but a physiology-matched, physiology-tuned device for reading the human brain with greater accuracy and intention than ever before.

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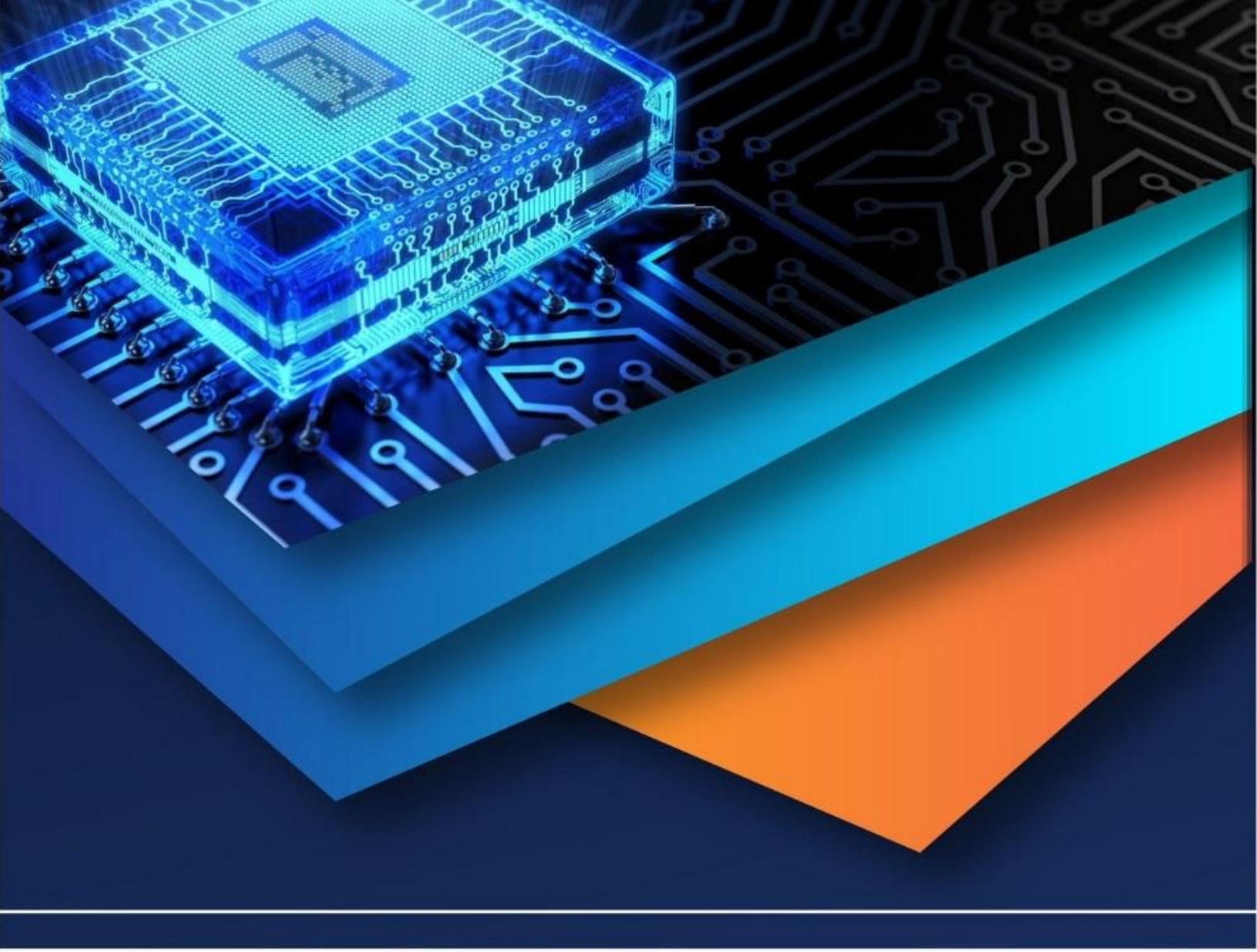
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