Data-Driven Methods in Simultaneous EEG-fPET-fMRI: Opportunities and Challenges

Penghui Du[1,2], Jingyuan E. Chen[1,3]
[1] Athinoula A. Martinos Center for Biomedical Imaging, Massachusetts General Brigham, Boston, MA, USA
[2] Neuro-X Section, Swiss Federal Technology Institute of Lausanne, Lausanne, Switzerland
[3] Department of Radiology, Harvard Medical School, Boston, USA

***Abstract*—Recent advances in human dynamic functional imaging now allow simultaneous tracking of electrophysiological activity (EEG), hemodynamic responses (fMRI), and metabolic fluctuations using a novel functional [^{18}F]-fluorodeoxyglucose PET technique (fPET-FDG). This tri-modal approach yields an exceptionally rich dataset that captures complementary physiological processes across distinct spatial and temporal scales. This conference paper addresses the analytical challenges and opportunities posed by such datasets, with a particular focus on time-resolved fusion methods capable of probing the intricate interplay among neuronal, hemodynamic, and metabolic dynamics. We first outline the specific signal characteristics and experimental design considerations for tri-modal EEG-fPET-fMRI acquisition. We then discuss existing and emerging approaches for time-resolved data integration and highlight methodological considerations for leveraging versatile, data-driven techniques to advance holistic interpretations of brain function.**

I. Introduction

Brain activity constantly reconfigures itself across multiple timescales, from milliseconds to minutes, to support large-scale information processing. This multi-scale activity triggers cascading physiological responses that can be captured by various dynamic functional imaging techniques. For instance, electroencephalography (EEG) measures rapid, millisecond-scale fluctuations in postsynaptic potentials [1], [2]. Functional Magnetic Resonance Imaging (fMRI) captures slower, second-scale changes in cerebral blood flow and oxygenation, which are driven by neurovascular coupling [3]. More recently, a functional Positron Emission Tomography (fPET) technique utilizing constant infusion of [^{18}F]-fluorodeoxyglucose (FDG)—termed fPET-FDG—has enabled the measurement of minute-scale fluctuations in glucose metabolism within a single scan session [4], [5]. Collectively, these modalities provide crucial, complementary views on brain function, each specializing in a distinct physiological process and operating at unique spatial and temporal scales.

These distinct physiological signals can now be acquired simultaneously by recording EEG inside an integrated PET-MRI scanner [6]–[10], offering a unique opportunity to observe electrophysiological, hemodynamic, and metabolic dynamics in concert. This capability opens the door to probing dynamic neuro-hemo-metabolic states underlying cognition and arousal.

In this conference paper, we focus specifically on tri-modal integration involving EEG, blood-oxygenation-level-dependent (BOLD)-fMRI, and fPET-FDG. The unusually rich information embedded in these datasets presents both opportunities and analytical challenges—namely, how to integrate signals that arise from distinct biological processes and unfold across disparate spatiotemporal scales to achieve a more holistic understanding of brain function. We review existing analytical efforts in this emerging domain and highlight promising avenues that can be explored by harnessing data-driven frameworks. We begin by outlining the signal characteristics of tri-modal acquisitions and associated experimental design considerations, then discuss potential analytical strategies and open opportunities for multi-modal fusion and for examining time-resolved (de)couplings among electrophysiological, hemodynamic, and metabolic processes.

II. Signal Characteristics

EEG measures the brain's electrical activity via voltage fluctuations recorded at the scalp. Its signals primarily arise from synchronous postsynaptic potentials in large populations of pyramidal neurons, whose aligned dendrites generate detectable extracellular fields [1], [2]. EEG offers excellent temporal resolution on the order of milliseconds, enabling precise tracking of rapid neuronal dynamics and oscillations across a broad frequency range. However, its spatial resolution is limited to the centimeter scale due to volume conduction and the difficulty in localizing deep or focal sources.

BOLD-fMRI measures hemodynamic fluctuations related to changes in blood oxygenation and flow, providing an indirect marker of neuronal activity. The BOLD response typically peaks several seconds after a stimulus, reflecting the slower dynamics of vascular physiology [3]. Modern acquisition strategies—such as simultaneous multi-slice imaging—enable whole-brain coverage at 2 mm isotropic spatial resolution with sub-second sampling, as used in many large-scale data initiatives [11], [12]. Although the resolution may be constrained by hardware factors like coil designs when acquired within a hybrid PET-MRI system [13], fMRI still offers a favorable balance of high spatial and moderate temporal resolution, outperforming both EEG and PET in spatial precision.

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FDG-PET measures glucose metabolism and is widely used to quantify metabolic activity in the brain and other organs. While conventional PET produces slow, static estimates, recent advances in scanner sensitivity and the introduction of constant-infusion paradigms have enabled fPET approaches that track minute-scale changes in glucose uptake [4]. Under constant infusion, fPET time-activity curves (TACs) show quasi-linear behavior, and stimulus-driven metabolic shifts appear as changes in TAC slope that can be modeled with high sensitivity. Several studies have demonstrated the ability of fPET-FDG to detect metabolic responses during sensory, cognitive, and arousal-related paradigms [5], [14]–[16]. Although the exact temporal impulse response of fPET-FDG is still under investigation, recent evidence suggests that this method can approach sub-minute temporal dynamics [17], posited to reflect signals linked to glucose supply rather than phosphorylation [18]. For this paper, we primarily focus on metabolic changes occurring on minute-level timescales.

Collectively, these modalities differ not only in their underlying biological sensitivities but also in their distinct and complementary spatiotemporal profiles (Fig. 1). Understanding these differences is essential for the design, interpretation, and integration of tri-modal imaging studies.

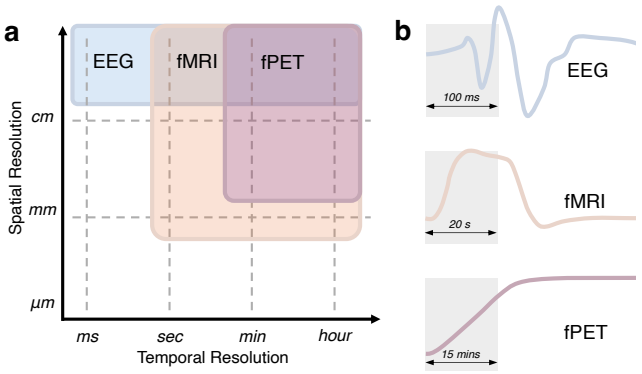

Fig. 1. Distinct spatiotemporal properties of EEG, BOLD-fMRI, and fPET-FDG. (a) Spatiotemporal resolution of the three modalities; (b) Exemplar stimulus-evoked responses measured by each modality; stimulus-on periods are indicated by shading.

III. Experimental Design

The design of tri-modal experiments can be broadly grouped into two main categories, as summarized in Fig. 2.

The first category employs mixed-design paradigms, which are particularly suitable for isolating spatiotemporal features of physiological activity tied to specific brain functions (e.g., sensory or cognitive stimuli). In these designs, identical stimuli are delivered at multiple timescales to maximize sensitivity across all three modalities simultaneously. The structure involves rapid millisecond-scale stimulus blocks (optimal for evoking electrophysiological potentials) nested within 10–20 s on/off task blocks (which efficiently entrain vascular responses), which are in turn embedded within 5–15 min on/off blocks to capture slower, minute-scale fPET metabolic responses. Standard model-based approaches—such as trial-averaging or the general linear model (GLM)—can then be applied to extract task-evoked brain responses across these distinct timescales.

The second category adopts a more flexible, unconstrained experimental framework, allowing ongoing or spontaneous changes in brain activity throughout the scan while each modality simultaneously tracks electrophysiology, hemodynamics, and metabolism. Examples include: (1) resting-state or spontaneous fluctuations in brain vigilance (including sleep); (2) pharmacological manipulations or anesthesia; and (3) naturalistic paradigms such as movie watching, auditory stimulation, or arousal/valence alternations. In these settings, state changes can be inferred from external markers (e.g., delivered stimuli or drug administration, or behavioral cues) or from simultaneous EEG measurements. Analyses therefore rely on more flexible, data-driven techniques that do not assume strict trial timing. They accommodate large-scale, continuous data and address challenges similar to those encountered in exploratory data mining contexts.

IV. Multi-Modal Fusion

Having introduced common experimental designs, we now turn to multi-modal fusion concepts that leverage information in the temporal domain. The approaches discussed below draw inspiration from two primary sources: (1) established simultaneous EEG–fMRI research [19]–[21], now extended by the inclusion of a third modality fPET; and (2) more generic data-driven frameworks that extract and compare static metrics per modality across large subject populations [22], [23].

A. Separate Analysis and Post Hoc Comparison

The simplest and most straightforward multi-modal fusion approach is to analyze each modality separately and then draw links or compare the corresponding signal patterns identified from the simultaneously acquired data (Fig. 3a). Initial feature extraction may rely on model-based methods (e.g., GLM-based task activation in mixed-design paradigms) or on data-driven approaches such as clustering or independent component analysis (ICA) [24], which extract spatial patterns along with their associated temporal dynamics of both signals and noise components. Cross-modal links can then be established post-hoc using prior knowledge (e.g., by referencing the timing of imposed stimuli or specific anatomical locations).

B. Asymmetric Data Integration

In lieu of analyzing each modality alone, it can be advantageous to leverage information extracted from one modality to guide or constrain the analysis of another, referred to as asymmetric data integration. Within the tri-modal imaging framework (Fig. 3b), this can be implemented in multiple directions. EEG measures can provide a ground-truth index of brain states to guide the exploration of state-dependent changes in hemodynamic and metabolic connectomes using fMRI and fPET [7]. Conversely, the high spatial resolution and whole-brain coverage of imaging modalities (particularly

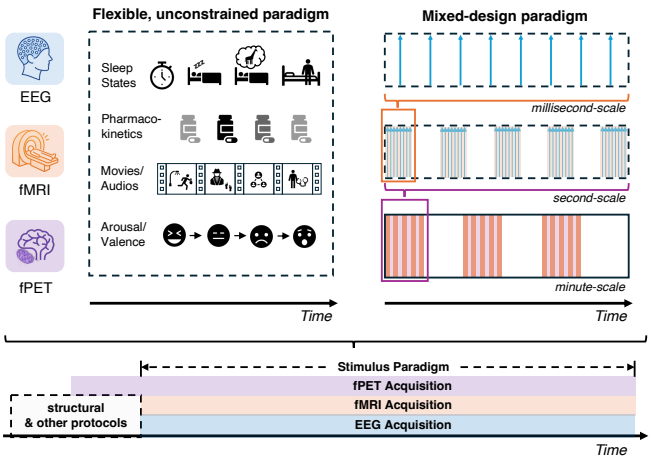

Fig. 2. Experimental designs for tri-modal imaging. Flexible, unconstrained paradigm: stimuli or conditions that span the entire recording, such as transitions between sleep states, pharmacokinetic effects, movie or auditory stimulation, or slowly varying arousal/valence states. Mixed-design paradigm: stimuli presented at nested timescales, in which brief events at fast timescales are embedded within longer blocks at slower timescales. This structure enables joint characterization of rapid electrophysiological responses alongside slower hemodynamic and metabolic dynamics.

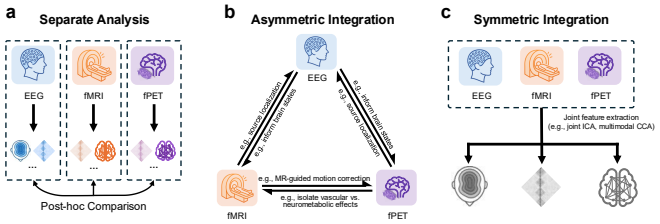

Fig. 3. Schemes of tri-modal fusion. (a) Separate analysis: each modality is analyzed independently, and the resulting maps or features are compared post hoc to identify shared or complementary information. (b) Asymmetric integration: information from one modality is used to constrain or guide the analysis of another modality. (c) Symmetric integration: all modalities are modeled jointly without designating any modality as primary, yielding fused cross-modal components or features.

fMRI) can inform and refine EEG source localization [25], [26]. In addition, beyond the use of high-resolution MRI for partial volume correction and image-derived arterial input functions, real-time, second-resolution motion estimates from dynamic fMRI time series can be used to correct for movements in PET signals [27].

C. Symmetric Data Integration

Complementary to asymmetric integration, symmetric data integration seeks to leverage the full spectrum of information contained within multimodal datasets [21]. These data-fusion approaches employ a common or jointly constrained model—typically implemented through machine-learning frameworks—to extract shared components across all modalities simultaneously (Fig. 3c). In the context of tri-modal EEG-fPET-fMRI acquisitions, particularly under flexible and unconstrained designs, such methods capture shared temporal or spatial structure by imposing explicit linkages among modality-specific signal sources.

1) Multi-Variate ICA: We use ICA as a primary example to illustrate these opportunities; see [22], [23] for comprehensive reviews of additional multivariate multimodal fusion methods, including Canonical Correlation Analysis (CCA), Partial Least Squares (PLS), and others. ICA is a widely used computational technique that separates complex multivariate signals into statistically independent, maximally non-Gaussian sources by identifying a linear, non-orthogonal transformation that minimizes dependencies among components. It is a powerful framework for uncovering latent brain networks and is readily extensible to multimodal data fusion. In tri-modal integration, correspondence across network components can be enforced through a spectrum of ICA frameworks that impose varying assumptions about linkages among mixing matrices (with loading or modulation either across subjects or time). For example, data from all modalities can be concatenated and decomposed with a joint ICA model that assumes strictly identical mixing matrices across modalities [28] (Fig. 4a). Alternatively, these assumptions can be relaxed by decomposing each modality separately while constraining correlations among the mixing matrices, as in multi-way parallel [29], [30] or linked ICA [31] (Fig. 4b). Overall, the diverse family of ICA and related multi-variate approaches provides substantial flexibility in incorporating different degrees of coupling across EEG, fMRI, and fPET.

Extending symmetric fusion models to tri-modal data, however, raises several fundamental challenges. A first issue arises from the highly unmatched spatiotemporal resolutions and dimensionalities across modalities. EEG features very sparse spatial sampling (number of channels) compared to the whole-brain voxel coverage of fPET/fMRI, yet it possesses a much higher temporal resolution (millisecond-scale) compared to fMRI (second-scale) and fPET (minute-scale). For ICA frameworks relying on temporal or spatial concatenation, this mismatch necessitates aggressive dimensionality reduction for all modalities. Such compression (e.g., aggressive temporal averaging) risks discarding the rich, high-temporal-resolution information from EEG and fMRI that motivates their acquisition.

An accompanying consideration is heterogeneity in signal scaling due to the distinct signal-to-noise ratio and noise properties. EEG and fMRI recordings are often modeled with autoregressive, approximately homoscedastic noise, whereas fPET signals are inherently heteroscedastic: because they reflect photon count statistics, they follow a quasi-Poisson process in which variance increases over time as FDG accumulates. These differences demand appropriate scaling and effective whitening steps during dimensionality reduction for each modality to ensure that the joint decomposition is not disproportionately dominated by one modality.

A third consideration—common to nearly all joint decomposition methods—concerns the assumption that components correspond across modalities, an assumption that rarely holds

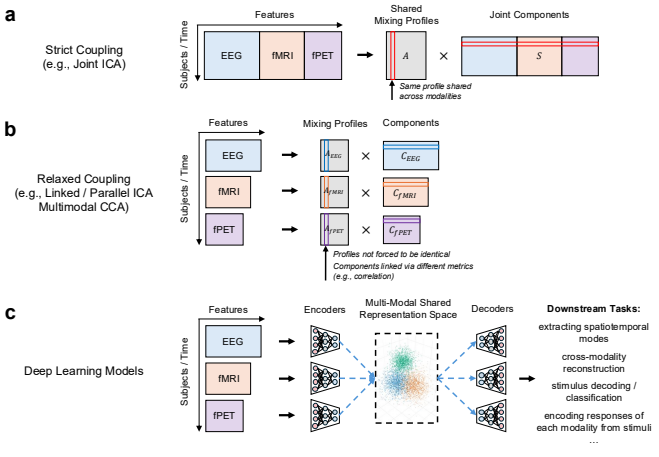

Fig. 4. Exemplar data-driven frameworks for symmetric integration. (a) Strict-coupling decompositions (e.g., joint ICA) impose a shared mixing profile across modalities, yielding components that are in strict one-to-one correspondence across EEG, fMRI, and fPET. (b) Relaxed-coupling decompositions (e.g., linked/parallel ICA, multimodal CCA) estimate modality-specific mixing profiles while introducing explicit or implicit coupling constraints, ensuring that corresponding components remain statistically associated. (c) Deep learning models that learn shared latent representations directly from multimodal data (e.g., multimodal autoencoders), which can be trained to extract spatiotemporal modes and to enable cross-modal encoding/decoding or other downstream tasks.

for many noise sources. Each modality exhibits distinct artifact structures: EEG is susceptible to muscle and ocular electrical activity and ballistocardiogram artifacts in the MRI environment; fMRI is confounded by cardiac- and respiration-driven vascular fluctuations; and PET is uniquely impacted by photon scattering, attenuation, and other count-based noise processes. Even noise sources shared across modalities, such as head motion, manifest in complex, modality-specific ways that may require targeted a priori correction. Consequently, effective joint decomposition approaches may rely on extensive preprocessing and artifact removal to better approximate the assumption that signal (and noise) components can be coherently estimated across EEG, fMRI, and fPET.

2) Deep Learning Approaches: In recent years, deep learning has advanced rapidly, driven by the increasing availability of large-scale data, computational resources, and powerful model architectures. These developments have motivated emerging interest in neuroimaging applications and have opened a promising pathway for multimodal fusion involving simultaneous EEG-fMRI-fPET. In particular, Transformer-based models have demonstrated superior performance in multimodal sequential signal analysis, such as fusing vision-language-audio modalities [32], making them especially well-suited for multimodal neuroimaging fusion. Such architectures hold strong potential to alleviate key challenges associated with mismatched spatiotemporal resolutions and heterogeneous noise statistics across modalities. Reflecting this trend, an increasing number of recent studies have begun to adopt Transformer-like frameworks for joint multimodal neural data analysis [33], [34]. As illustrated in Fig. 4c, these models typically project heterogeneous, modality-specific inputs into a shared latent representation via dedicated encoders and then decode task-relevant representations through task-driven decoders. This unified framework supports a broad range of downstream applications, including spatiotemporal mode extraction, cross-modality reconstruction, and stimulus decoding or classification.

Compared with classical model-driven approaches, deep learning relies less on strong prior assumptions about neural signal generation mechanisms but faces challenges related to the limited availability of large-scale concurrent multimodal datasets and the interpretability of learned representations. Nevertheless, with growing understanding of the signal and noise characteristics of EEG, fMRI, and fPET, generating high-quality synthetic multimodal datasets is becoming increasingly feasible. Such synthetic data can substantially expand the available training data for multimodal fusion models, while providing controllable conditions that facilitate the evaluation and improvement of model interpretability. Although still in its early stages, deep learning-based tri-modal fusion represents a compelling and highly promising direction for future research.

V. Time-Resolved Couplings Across Modalities

After identifying relevant features from each modality, the subsequent step is to examine the dynamic interactions among these signals. When attempting to unify all physiological information onto a common timescale to study their time-dependent interplay, the temporal resolution is inevitably constrained by the slowest modality—typically the minute-scale metabolic changes captured by fPET.

A. Temporal Alignment via Collapsing Fast Modalities

A straightforward and established approach is to collapse rapid EEG (millisecond-scale) and fMRI (second-scale) measurements to match the slower temporal resolution of fPET signals, as depicted in Fig. 5a. This involves summing or averaging the brain activity of interest (e.g., power of specific EEG oscillations or fMRI fluctuation amplitude) within non-overlapping windows that correspond to fPET time points. Using this method, existing studies have revealed tight temporal coupling between task-evoked blood flow and glucose consumption in the primary visual cortex during flickering-checkerboard stimulation [35], as well as the co-evolution of electrophysiological, hemodynamic, and metabolic activity during the descent from wakefulness into sleep [7]. Since fPET-FDG signals accumulate over time, statistical associations can be examined in two complementary ways: by correlating collapsed EEG or fMRI measures with the temporal derivatives of dynamic fPET TACs, or by correlating the temporal integrals of EEG/fMRI summary metrics—mimicking the accumulation kinetics of FDG—with the dynamic fPET TACs [7], [35]. This collapsing approach can also be applied to investigate variations in physiological dynamics associated with specific task blocks, such as trial-by-trial effects including errors, reaction time, adaptation, or fatigue.

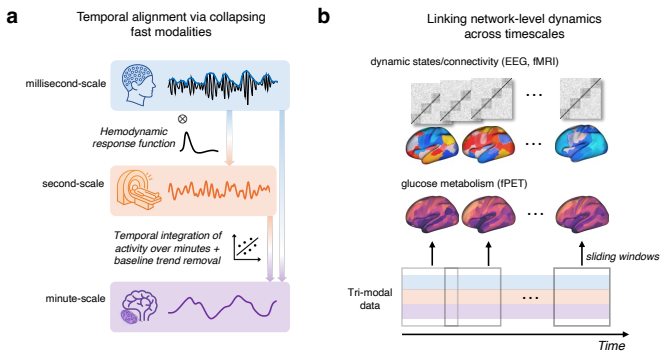

Fig. 5. Time-resolved couplings across modalities. (a) Temporal alignment by collapsing fast modalities: EEG/fMRI activity is integrated over time to match the timescale of fPET, enabling the examination of dynamic (de)coupling across modalities. (b) Linking network-level dynamics across timescales: network metrics derived from fast-timescale EEG–fMRI activity are related to snapshots of glucose consumption estimated over minute-long sliding windows, allowing investigation of how energetic costs relate to large-scale network dynamics.

B. Preserving Multi-Timescale Dynamics

While the temporal-collapsing approach is straightforward, it inherently omits the rich repertoire of brain network dynamics occurring at sub-minute timescales—the very reason EEG and fMRI are acquired at high temporal resolution. An alternative strategy, as presented in Fig. 5b, is to preserve signal dynamics across timescales by focusing on characterizing network-level features rather than strictly unifying the timescales of raw signals. For instance, specific network characteristics—such as EEG microstates [36], connectome [37], or fMRI dynamic functional connectivity [38] (including summary metrics like dwell times or transition trajectories)—can be linked to corresponding "snapshots" of glucose consumption estimated from fPET. This approach allows for the study of cross-modal interactions while retaining the temporal richness and complexity of each individual modality.

VI. Conclusions

In summary, simultaneous EEG-fPET-fMRI offers a promising new window into the neuro-hemo-metabolic dynamics that support large-scale brain computation underlying cognition, arousal, and disease. As a field still in its early stages, substantial opportunities remain for data-driven methods to fully harness the unusually rich information contained in these tri-modal datasets. While the complexity of integrating signals across disparate spatial and temporal scales poses analytical challenges, it creates new opportunities for sophisticated data-fusion frameworks. With continued methodological development, this tri-modal framework has the potential to yield a more comprehensive and holistic understanding of the brain's dynamic functional architecture in health and disease.

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