Inferring Macroscale Brain Dynamics via Fusion of Simultaneous EEG/fMRI

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Abstract

Advances in the instrumentation and signal processing for simultaneously acquiring electroencephalography and function magnetic resonance imaging (EEG/fMRI) have opened up the exciting possibility of new ways to observe the spatiotemporal neural dynamics of the human brain at the macro-scale. Central to the utility of EEG/fMRI neuroimaging systems are the methods for fusing the two data streams, specifically the underlying assumptions those methods adopt, as well as the shared and unique neural substrates and latent factors they hope to uncover. Machine learning plays a key role in fusing EEG/fMRI, with approaches roughly dichotomized into those which are symmetric and asymmetric in terms of how the two modalities are used to inform the analysis. Studies using these approaches have shown that fusion has yielded new insights into brain function which are not possible when each modality is acquired separately. As technology improves and methods for fusion become more sophisticated, the future of EEG/fMRI for non-invasive measurement of brain dynamics include meso-scale mapping at ultra-high MR fields, targeted perturbation-based neuroimaging, and the use of deep learning to uncover non-linear representations that link the electrophysiological and hemodynamic measurements.

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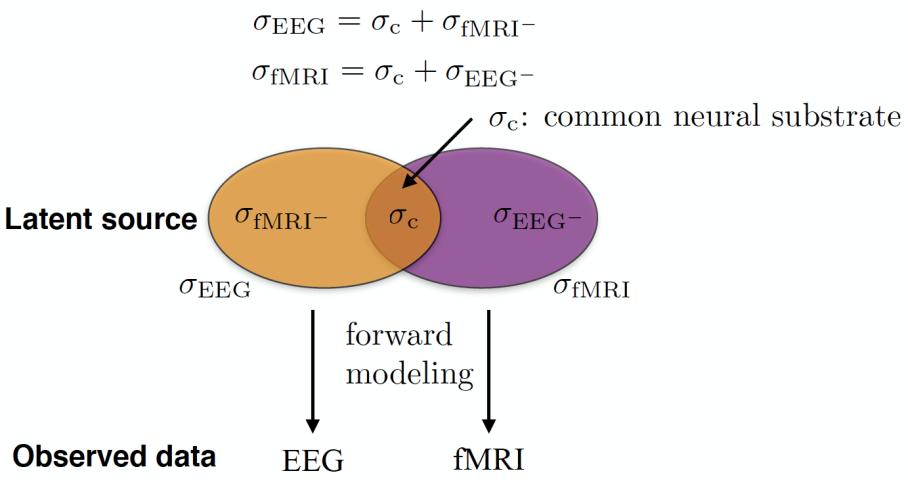
1. INTRODUCTION

Electroencephalography (EEG) and functional magnetic resonance imaging (fMRI) are two non-invasive neuroimaging modalities that are ubiquitously employed in human neuroscience (Bridwell et al. 2018, Detre & Floyd 2001, da Silva 2013, Li et al. 2009). Well-known is that the two modalities complement one another in terms of their spatial and temporal resolution, and this has thus led to the development of systems capable of simultaneously acquiring EEG and fMRI. Though theoretically appealing as a method for multimodal brain imaging, simultaneously acquired EEG and fMRI (EEG/fMRI) is still sparingly utilized relative to its constituent modalities.

Originally this under utilization was largely traced to the technical hurdles related to the electromagnetic interference induced on each modality by the other. However improvements in the electronics and electromagentic shielding, as well as better signal processing, has substantially improved the quality of data acquired via EEG/fMRI (Sajda et al. 2010). The main challenge is no longer the technical difficulty in concurrent data acquisition, but rather the lack of efficient and principled methods for fusing the data, specifically, tools capable of optimally combining the information from the two modalities with high fidelity while recognizing their unique strengths and weaknesses.

Broadly, EEG/fMRI data fusion methods fall into two categories (Huster et al. 2012, Valdes-Sosa et al. 2009, Rosa et al. 2010a, Abreu et al. 2018, Sui et al. 2012): asymmetric fusion and symmetric fusion. If one modality is treated as a prior or constraint to guide the analysis of the other modality, the fusion is asymmetric. Alternatively, if the information from each modality is used in an egalitarian manner, the fusion is symmetric. Symmetric fusion can be further divided into two categories: model-driven and data-driven. In model-driven approaches, EEG and fMRI are integrated in a generative framework by explicitly modeling the neurovascular coupling through their common neural substrates. Data-driven approaches, on the other hand, avoid the complex modeling of the generative processes of the EEG and fMRI. Instead, they directly exploit the covariance between EEG and fMRI in the feature space using some computational machinery, regardless of the differences that might exist in their underlying biophysical properties.

In this review we focus on the methods that have been and are being developed for fusion of EEG/fMRI. We begin with a brief discussion of the two modalities in terms of what they measure and how, when collected simultaneously, artifacts are introduced due to



Adapted from Rosa, M. J. et al. (2010).

Figure 1

EEG and fMRI can be viewed as measuring both unique and common neural activity. Some methods for fusion focus on the underlying common neural activity σ_c, while others also consider the unique information (σ_{EEG-}, σ_{fMRI-})

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electromagnetic coupling. We then review the state-of-the-art in fusing the two modalities within the context of symmetric and asymmetric approaches. We emphasize that some approaches focus primarily on activity that represents a common neural substrate measurable by the two modalities (σ_c, Fig 1) while others also consider the unique information that each modality captures (σ_{EEG-}, σ_{fMRI-}). We provide examples of how the different methods have yielded insight into the spatiotemporal dynamics in the human brain that would not be possible for cases where these modalities are acquired on their own.

2. ACQUISITION OF EEG/FMRI

EEG measures the electrical activity, from electrodes on the scalp, generated by the synchronized depolarization of populations of neurons. The major contributor of the measured scalp EEG is the postsynaptic potentials of the large pyramidal neurons in the cortex (Kirschstein & Köhling 2009). Inferring the underlying sources of the scalp EEG is challenging due to volume conduction (van den Broek et al. 1998), given that a measurement at an electrode is a summation of multiple neural sources, including those that are distal from the recording electrode.

Therefore, the major limitation of scalp EEG is the lack of spatial resolution (Burle et al. 2015). Nevertheless, EEG can provide temporally resolved brain dynamics on a millisecond scale (Michel & Murray 2012). Blood oxygenation level dependent (BOLD) fMRI, on the other hand, measures inhomogeneities in the magnetic field due to changes in the level of oxygenated hemoglobin in the blood flow across the entire brain volume (Logothetis &

Wandell 2004). fMRI BOLD activity reflects the blood oxygenation changes in response to the oxygen consumption by active neurons. The coupling between the neural activity and BOLD response is still unclear, however, several studies have suggested that BOLD signal is correlated with slow-varying postsynaptic activity as opposed to action potentials (de Munck et al. 2009, Tyvaert et al. 2008). There is emerging evidence that BOLD signal links to the power of EEG at different frequency bands (Rosa et al. 2010b, Leite et al. 2013). A key feature of the BOLD signal is that it is a delayed and temporally blurred hemodynamic response of the leading neural activity (Arthurs & Boniface 2002). Despite the high spatial resolution and whole-brain coverage, the poor temporal resolution of fMRI along with regional variations in hemodynamic response pose a significant challenge in the analysis of fMRI data (Logothetis 2008).

EEG/fMRI acquisition is aimed at providing non-invasive imaging of the human brain with high temporal specificity and anatomical localization; something that is difficult, if not impossible to achieve by either modality alone (Uludağ & Roebroeck 2014, Vitali et al. 2015). However, the combined benefits come at the cost of a reduced signal-to-noise ratio (SNR) in both modalities when they are collected simultaneously (Laufs 2012). Compared to stand-alone EEG, EEG collected inside MR scanner exhibits two types of large and periodic artifacts: gradient artifacts and ballistocardiogram (BCG) artifacts (Allen et al. 2000). Gradient artifacts are caused by the switching of the gradient magnetic field and typically are much larger in magnitude compared to EEG activity. Successful gradient artifact removal requires MR compatible EEG amplifiers that do not saturate for these large artifacts and remain in the linear range, as well as synchronization between the EEG clock and MR scanner clock such that an accurate average template of the artifact can be obtained and used to subtract out the artifact (Mullinger et al. 2011). BCG artifacts are more complicated and problematic in that simple subtraction techniques are less effective since the artifacts are highly non-linear across the scalp and the frequency content of the artifact overlaps with the EEG signal. BCG largely arises from the pulsatile movements of the EEG electrodes that are synchronized to the cardiac cycle (Debener et al. 2008). A widely used conservative method for removing BCG artifacts is based on principle component analysis (PCA) (Niazy et al. 2005). The method is conservative in that it typically tolerates residual BCG in favor of minimally effecting the underlying EEG. Figure 2 illustrates the gradient and BCG artifacts and what are considered clean EEG signals after these artifacts are removed.

Ballistocardiogram: An artifact in the EEG, induced by the static field of the MR machine, which is non-linear and driven by pulsatile blood flow and movement.

Though many consider the artifacts induced in the EEG by the MRI to be the most significant and problematic in terms of further analysis and fusion of the data, one must be aware that EEG also induces artifacts in the fMRI data that is collected. The BOLD signal is relatively small – about a 1-5% signal change for an active task (Biswal et al. 2007). The presence of EEG wires and scalp electrodes increases the magnetic field inhomogeneity and thus leads to reduced SNR in the BOLD signal, especially near the top of the head where the wire bundle on EEG cap exits the ME head-coil. Figure 3 shows an example of several fMRI slices for a BOLD image acquired with an EEG system in the MRI scanner. In most cases bias field correction techniques can be used to improve the SNR of the BOLD data.

In general, over the last decade or so, substantial research and technology development has gone into creating solutions for removing artifacts, reducing noise and preprocessing the data from EEG/fMRI recordings (Marino et al. 2018, Shams et al. 2015, Nakamura et al. 2006, Negishi et al. 2004, Ritter et al. 2007, McIntosh et al. 2020, Chowdhury et al. 2014). Given these higher SNR data, we focus our remaining discussion on how they can be fused

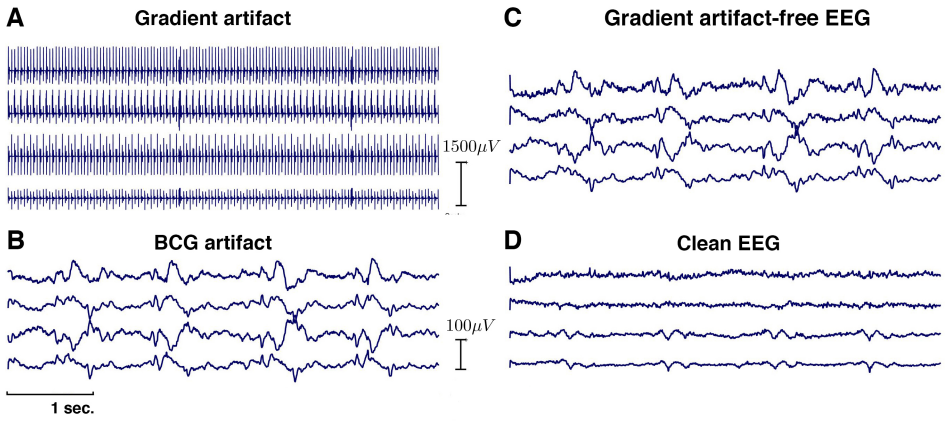

Figure 2

Illustration of the gradient and BCG artifacts. (A) Gradient artifact. (B) BCG artifact. (C) EEG signal after gradient artifact is removed. (D) Cleaned EEG signal without gradient and BCG artifacts. The gradient artifact is about 10 times larger in magnitude compared to the BCG artifact and true neural signals.

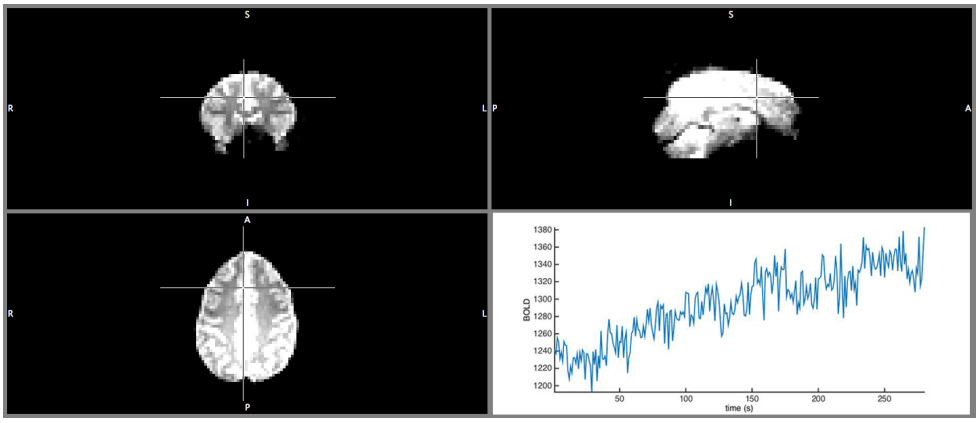

Figure 3

Example slices of a BOLD volume and the time series at one voxel. Hyper-intensity at the top of the brain is a result of electromagetic interference of the EEG electrodes.

in ways that yield insight into brain function.

3. FUSING EEG/fMRI

3.1. Background

Asymmetric fusion refers to methods where information of one modality is used as a prior or weighting for the other modality. For example, EEG information (e.g. amplitude, frequency, and phase) can be incorporated as BOLD predictors in the general linear model (GLM) analysis of fMRI (Zotev et al. 2014, Murta et al. 2015, Warbrick et al. 2014,

Symmetric fusion: Information from the neuroimaging modalities is used to mutually constrain one another.

Asymmetric fusion: Information of one neuroimaging modality is used as a prior or weighting for analysis of the other modality.

Baumeister et al. 2014, Ito et al. 2020, Green & Heekeren 2009, Bayer et al. 2018, Herweg et al. 2016, Walz et al. 2015a, Muraskin et al. 2016a,b, McMillan et al. 2020, Uji et al. 2018, Iannaccone et al. 2015, Zotev et al. 2018). This EEG-informed fMRI analysis often takes advantage of the single-trial EEG variability. Single-trial EEG variability can be derived at different time intervals within the temporal span of a trial, thus making it possible to assign temporal order to fMRI activations. Conversely, fMRI activation maps can be used as a spatial constraint for EEG source localization (Babiloni et al. 2000, Dale et al. 2000, Ou et al. 2010, Henson et al. 2010, Lei et al. 2015). The fMRI-informed EEG analysis increases the spatial specificity of EEG source localization by confining the source space in the EEG inverse problem.

Latent source: Unobserved neural activity that is the source of the EEG and/or fMRI measurement.

When EEG and fMRI information are combined equally, the fusion is symmetric. Model-driven symmetric fusion seeks to model the shared but unobserved neural states which give rise to EEG and fMRI. For example, several studies have employed state-space models to link the temporal evolution of latent neural dynamics with joint EEG and fMRI observations via their own biophysical generative processes (Valdes-Sosa et al. 2009, Rosa et al. 2010a, Riera et al. 2006, Jun et al. 2008, Deneux & Faugeras 2010, Purdon et al. 2010, Lenz et al. 2011, Daunizeau et al. 2007). This type of models aim at making inferences directly on the shared latent brain states given EEG and fMRI observations. Data-driven symmetric fusion refers to a broad range of approaches where machine learning methods, such as Independent Component Analysis (ICA) and linear regression are used to combine EEG and fMRI in a common feature space (Mantini et al. 2010, 2007, Schmüser et al. 2014, Horovitz et al. 2008, Britz et al. 2010, Novitskiy et al. 2011, Lei et al. 2011). These approaches typically do not employ physiological assumptions regarding the EEG and fMRI. In ICA-based EEG-fMRI fusion (Mijović et al. 2012), for instance, temporal EEG information and spatial fMRI information are concatenated as a single feature matrix and a joint ICA decomposition is performed across subjects. This technique generates spatial and temporal independent components simultaneously.

Asymmetric fusion approaches impose strong a priori assumptions about the covariability underlying EEG and fMRI but typically yield results that are readily interpretable. Data-driven approaches are flexible to extend to integrate EEG-fMRI with other modalities and therefore they are more suited for exploratory data mining tasks. Model-driven approaches which directly model the neurovascular coupling between EEG and fMRI are quite powerful, however, inference in such models is very challenging due to the high computational complexity of the numerical methods involved. Next, we present examples of the strength of each data fusion approach and consider the methods based on the nature of the specific research questions at hand.

3.2. Asymmetric fusion

EEG-informed fMRI approaches are the most extensively used methods in combining the two modalities. These approaches assume a coincident relationship between the neural substrates of EEG and fMRI. To leverage EEG information in fMRI analyses, features of interest are first extracted from EEG data and then used to construct regressors to explain the variance exhibited in fMRI data. For example, in an event-related EEG/fMRI design, features of the event-related potential (ERP) can be extracted from EEG on a trial-to-trial basis. On each trial, the feature value is used to modulate the event amplitude in the regressor time courses where each event is modeled as a stick function with the

duration and onset time aligned to each stimulus presentation. The regressor time courses are typically convolved with the hemodynamic response function of fMRI in the voxel-wise GLM modeling. It is noteworthy that this approach assumes a linear relationship between the EEG features and BOLD responses which is one manifestation of the neuro-vascular coupling.

Variations in the extracted ERP features will be driven by the EEG neural substrate σ_{EEG}, which contributes to the information shared with fMRI (σ_c) and the information unique to EEG (σ_{fMRI-}). Since it is difficult to isolate the contribution of the common neural substrate σ_c from σ_{EEG}, the variance in fMRI data explained by EEG regressors might be attributable to the neural substrate orthogonal to fMRI. This could potentially lead to biased interpretation on the fMRI results in EEG-informed fMRI analyses. Although the explanatory power of EEG regressors are confounded by EEG artifacts and the underlying neural activity that does not contribute to the hemodynamic response (neuro-vascular decoupling), the value of EEG regressors arises from the added temporal specificity absent in conventional fMRI analyses.

Various forms of EEG features can be extracted using either univariate or multivariate approaches, depending on the question of interest and underlying hypotheses on the EEG-fMRI relationship. We will focus the discussion on event-related EEG-fMRI stud. One useful approach for event-related designs is to extract single-trial variability from multi-electrode EEG signals at different time windows within the time span of the trial. These temporal EEG components usually exhibit trial-by-trial variability corresponding to distinct neural substrates. By constructing parametric EEG regressors from these component, the spatiotemporal dynamics of different neural substrates can be decoupled in fMRI.

This type of fusion, is by far the most prevalent in the literature and it has been used to study a wide range of cognitive processes (Fouragnan et al. 2015, 2017, Pisauro et al. 2017, Gherman & Philiastides 2018, Walz et al. 2013, 2015b, Tu & Sajda 2018, Muraskin et al. 2018, Pereira et al. 2020, Iannaccone et al. 2015, Green et al. 2017, Castelhano et al. 2014). For example, (Fouragnan et al. 2015) used this approach to infer the network dynamics associated with outcome valence (e.g. positive vs negative) during a reinforcement learning task. In a conventional fMRI study, one would typically contrast feedback-locked data from positive versus negative outcome trials. This in turn leads to a distributed set of differential activations (i.e. positive > negative and vice versa; Fig.4a). Neural networks, however, are more than localized activations and instead must also be defined in terms of their relative timing and their interactions. Moreover, categorical contrasts – such as the one described here – can only reveal relative differences, without information on the extent to which individual conditions can independently explain the fMRI signal.

Single-trial variability: Variation of neural measurements across similar trial-types that relates to intrinsic noise and/or an underlying latent source or neural substrate.

To address these issues EEG-informed fMRI leverages single-trial variability in electrophysiologically-derived temporal components to tease apart cascades of relevant neural processes in the fMRI. In this example, the authors reported two temporally-specific EEG components discriminating positive versus negative outcomes, occurring in rapid succession – 220 and 300ms – following feedback. Using the residualized trial-by-trial variability in these components the authors could introduce four separate fMRI predictors – one for each of the"Early"/"Late" EEG components and positive/negative outcome trials. In doing so, they were able to decouple the activations observed in the conventional fMRI contrast, thereby offering temporal order to the underlying networks (Fig.4b).

Specifically, they revealed the presence of a fast (Early) system comprising regions implicated in generating states of autonomic arousal that control immediate behavioral

(avoidance) responses following specifically negative outcomes (Critchley et al. 2003, Kerns et al. 2004, Philiastides et al. 2010b, Fouragnan et al. 2018). In contrast, a more deliberate (Late) system responds along the full continuum of negative and positive outcomes and is linked to brain regions that play a crucial role in reward processing and value-guided learning (Clithero & Rangel 2014, Philiastides et al. 2010a, Liu et al. 2011, Fouragnan et al. 2018).

Crucially, in both of these systems there were additional brain nodes, absent from the original fMRI contrast, further highlighting that endogenous variability in EEG-derived fMRI predictors could provide additional explanatory power compared to stimulus- or behaviorally-derived measures. Similarly, a potentially important advantage of such EEG-informed fMRI analysis is that it could reveal activations within deeper/subcortical structures – which are often missed due to their smaller size and lower signal-to-noise ratio – provide their BOLD activity covaries with the trial-by-trial variability of the cortical sources of the EEG signal.

Finally, having separated out the Early and Late systems, the authors could make more informed decisions on how to characterize the node interactions within as well as across the two systems. Of particular note, was a reliable thalamostriatal interplay whereby the thalamus (of the Early system) was downregulating activity in the ventral striatum (of the Late system) following negative outcomes, consistent with a mechanism of value updating. Correspondingly, individuals exhibiting stronger thalamostriatal coupling showed a higher rate of switching behavior and a tendency to weigh recent negative outcomes more strongly.

In another example, (Muraskin et al. 2018) used EEG-informed fMRI to offer a dynamic network reconstruction of rapid perceptual (visual) decisions. Decision-making depends on coordinated patterns of neural activity cascading across early sensory areas to higher-level executive systems, unfolding in time from the onset of a perceptual stimulus to the final commitment to a choice (Philiastides & Sajda 2007, Heekeren et al. 2008, Walz et al. 2014). Experimental paradigms often involve a parametric manipulation of decision difficulty (via adjustments to the difficulty of the external stimulus) and rely on fMRI contrasts between easy and more difficult trials to expose the underlying networks.

This approach, however, will produce an activation map of all brain regions that are sensitive to the level of stimulus evidence regardless of (functionally significant) differences in their temporal and response profiles (e.g., early differences in the level of phasic activation versus downstream differences in the rate of evidence accumulation). Consistent with this shortcoming, the authors demonstrated that a traditional fMRI predictor based on the amount of sensory evidence (i.e. easy > difficult trials and vice versa) resulted in a broad range of "static" activations, spanning the whole hierarchy of brain architecture (Fig.5a).

As in the previous example, these authors first extracted trial-by-trial variability from EEG components discriminating between easy and difficult trials, in the time interval between the stimulus onset and the response. While the discriminating information persisted across the entire trial, the trial-by-trial variability decoupled differently as time evolved, suggestive of a cascade of different processes. This continuous electrophysiological (endogenous) variability was then used to uniquely "tag" individual fMRI voxels with a "time" or set of times, via an encoding model that was fit to predict the trial-by-trial variability in the fMRI signal.

This EEG-informed "tagging" procedure revealed a progression of activity, which started shortly after stimulus presentation and proceeded simultaneously down the dorsal and ventral visual streams and lasted roughly up to 250 ms post-stimulus. After that the cascade

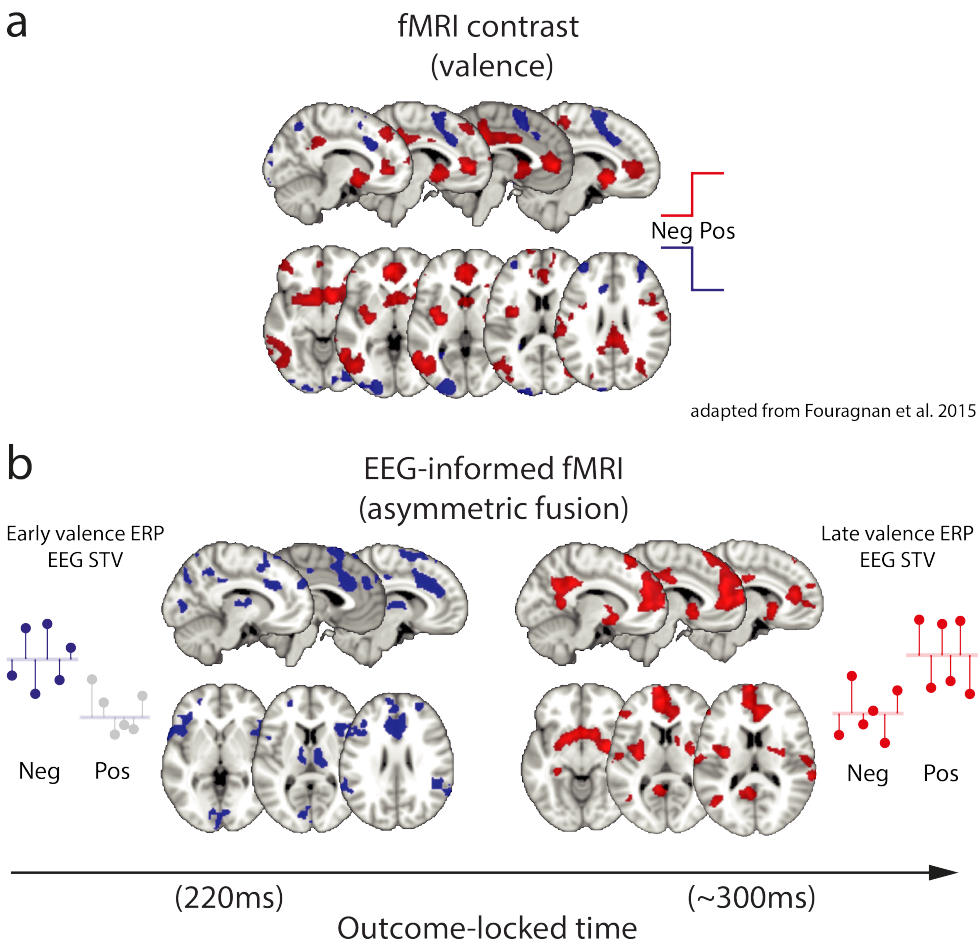

Figure 4

Asymmetric EEG-fMRI fusion during reinforcement learning (Fouragnan et al. 2015). (a) Conventional fMRI contrast between positive versus negative feedback trials, revealing a highly distributed, albeit "static", set of brain activations. Some brain regions are exhibiting stronger responses for positive than negative outcomes (red clusters) and vice versa (blue clusters) (b) Single-trial variability (STV) from two temporally distinct EEG components – and separately for positive and negative outcomes – are used as fMRI predictors to temporally decouple the activations seen in (a). Blue clusters are modulated primarily by STV in the earlier EEG component, following negative outcomes only. Red clusters are modulated by STV in the later EEG component along the full range of negative to positive outcomes.

became more complex and engaged regions of the parietal cortex as well as the medial prefrontal cortex, unfolding continuously until the time of response (Fig.5b). These regions are broadly consistent with previous reports in the literature (Heekeren et al. 2004, Philiastides et al. 2011, Philiastides & Sajda 2007), however, this approach enabled assignment of temporal order to the underlying networks in a way that was previously only possible with invasive techniques.

Another critical outcome of this work, was that a number of the relevant brain nodes appeared to be reactivated shortly after the response, though with opposite encoding weights (i.e. strongest for difficult compared to easier trials). Importantly, this inverse reactivation pattern would have been integrated across time and cancelled out in a conventional fMRI analysis (with a single "difficulty" predictor). Though this type of reactivation pattern is believed to be important for memory consolidation (Deuker et al. 2013) and post-decision metacognitive appraisal (Fleming et al. 2012, Gherman & Philiastides 2015), direct evidence in humans was lacking.

In this study, the authors could correlate the strength of this reactivation pattern with a proxy of decision confidence and demonstrate that this association was stronger for more difficult trials (i.e. when metacognitive appraisal is most beneficial for updating beliefs) and that it was mediated primarily by regions of the lateral prefrontal cortex previously implicated in metacognitive judgements (Fleming et al. 2012, Yeung & Summerfield 2012, Gherman & Philiastides 2018). Thus, this analysis offered concrete evidence that while in the process of making and executing a perceptual decision, the brain may replay activity to develop accurate metacognitive representations relevant for learning and adaptive behavior.

Both examples highlighted above, clearly illustrate that EEG-informed fMRI can lead to a rich set of observations, over and above what could be inferred by each modality alone. As such, leveraging electrophysiological variability to drive the analysis of functional data could be used to map temporal dynamics of neural information processing onto spatially well-defined networks (Debener et al. 2006) in a way that enables new insights and neuroscientific discoveries.

3.3. Symmetric fusion

To avoid a bias in inferring σ_c caused by the imbalanced use of information from each modality, symmetric fusion integrates information from EEG and fMRI equally. Symmetric fusion can be further categorized into model-driven and data-driven approaches. In model-driven approaches, EEG and fMRI are integrated in a common probabilistic framework where their shared neural substrate σ_c translates to EEG and fMRI observations explicitly via their own biophysical generative process. While this approach allows one to model and infer σ_c directly, several challenges arise, including the choice of the forward models for EEG and fMRI, the spatiotemporal dimensionality mismatch between EEG, fMRI and neuronal responses, and the difficulty in effective model inversion. There has been ongoing effort focused on developing a theoretical framework for the biophysical models of neuro-vascular coupling. For example, Riera et al. (Riera et al. 2007, 2006) proposed a Bayesian local electrovascular coupling model to infer the unknown neural states using simultaneous EEG-fMRI data. Daunizeau et al. (Daunizeau et al. 2007) proposed a variational Bayesian approach to infer the common EEG/fMRI sources from event-related bioelectric and hemodynamic responses. In their generative model, EEG sources share a common spatial profile with fMRI sources.

In contrast with model-driven approaches, data-driven approaches avoid the need of explicit generative models for neuro-vascular coupling. They rely on machine learning algorithms that operate in the "feature space" of EEG and fMRI and often make no specific assumptions on the common neural substrate σ_c. Therefore, information from EEG and fMRI is fully examined to uncover possibly shared covariance between them. One approach for data-driven approaches is to consider a classification analysis where classifiers are trained

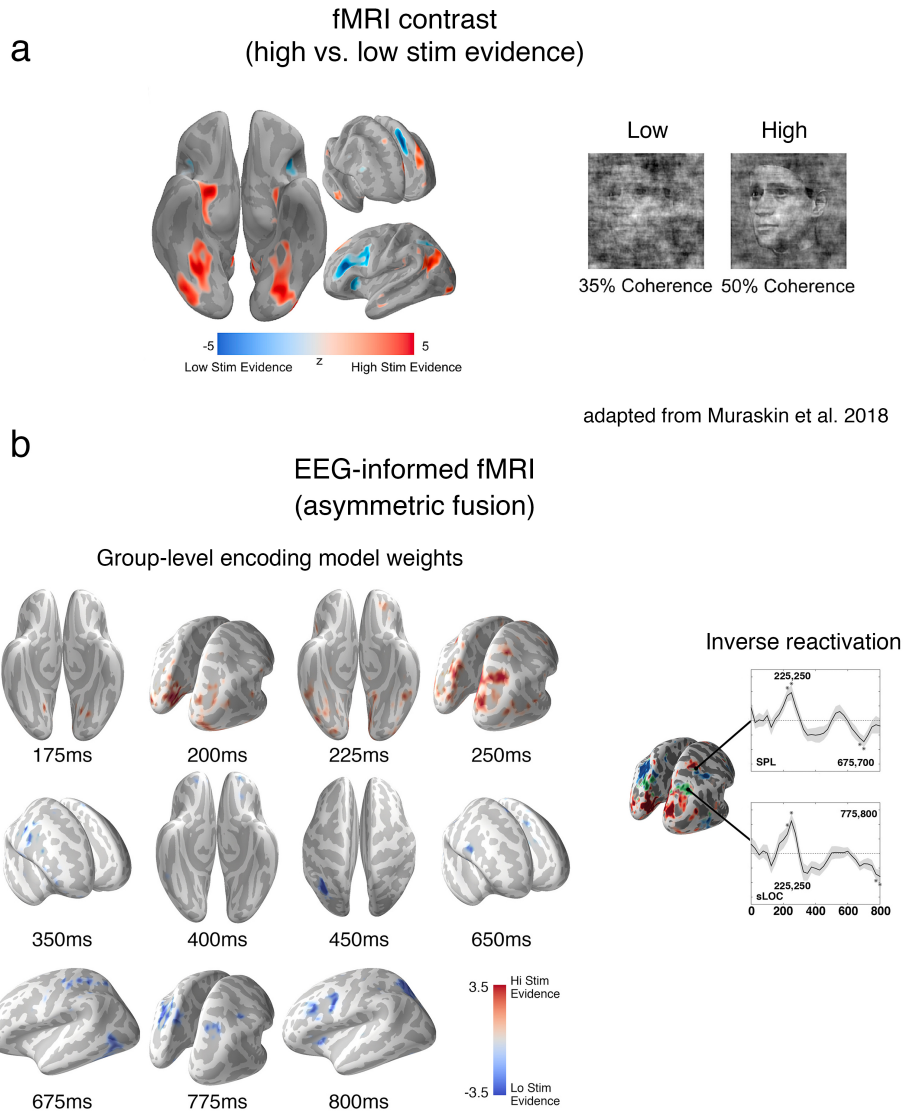

Figure 5

Asymmetric EEG-fMRI fusion during perceptual decision making (Muraskin et al. 2018). (a) Conventional fMRI contrast between high stimulus evidence (easy) versus low stimulus evidence (difficult) trials, revealing a highly distributed, albeit "static", set of brain activations. Some brain regions are exhibiting stronger responses for easy than difficult trials (red clusters) and vice versa (blue clusters), (b) Single-trial variability (STV) from continuous EEG components discriminating easy versus difficult trials was used in an encoding model to predict trial-by-trial variability in the fMRI, thereby decoupling the activations in (a) by "time-stamping" individual voxels. Inset: example of brain nodes with inverse reactivation profiles at different points during the decision process. Given the sluggish nature of the fMRI signal these reactivations would have cancelled each other out in a conventional (single predictor) fMRI analysis.

in the space of the individual modalities but linked via a cost function that encourages similarity in the trial-to-trial variability (Conroy et al. 2013). For example, given a multimodal dataset $(E_1, F_1, y_1), \ldots, (E_N, F_N, y_N)$, where for each trial i we have p_E EEG features $E_i \in \mathbb{R}^{p_E}$, p_F fMRI data $F_i \in \mathbb{R}^{p_F}$, and a trial label y_i that encodes information about, for example, the stimulus condition. For simplicity, consider the binary discrimination case, where $y_n \in \{0, +1\}$, and we have arbitrary features for each modality–e.g. E_i may be electrode voltages over a given time-window, or spectral power from particular frequency bands, and F_i may be the BOLD response from voxels from a region-of-interest (ROI). The approach then focuses on balancing two goals: (a) to design multivariate classifiers within each modality that can predict the trial labels; and (b) have these classifiers share similar patterns of trial-to-trial variability–i.e. the predictions output from each modality should be correlated.

Specifically, one can learn linear projections of the EEG data $v \in \mathbb{R}^{p_E}$ and of the fMRI data $w \in \mathbb{R}^{p_F}$ such that the joint component across modalities $E^T v + F^T w$ is predictive of the trial label vector y, and also the modality subcomponents $E^T v$ and $F^T w$ are correlated. This can be achieved by minimizing an objective of the form:

$$(v^*, w^*) = \arg\min_{v,w} \ell(y, E^T + F^T) + \lambda_L D(E^T v, F^T w) \quad 1.$$

where $\ell(.,.)$ is a classifier loss function, $D(.,.)$ measures dissimilarity between modalities and λ is a trade-off parameter.

In (Conroy et al. 2013) the authors evaluated the differences in between symmetrically linking the EEG and fMRI classifiers versus no linkage. Using EEG/fMRI data from (Muraskin) they found that with the exception of the Right Superior Frontal Gyrus, the unlinked method identified very similar areas. This suggests that the increased inter-modality correlation is explained less by identifying new areas, and more by altering the fine-grained patterns within the networks, in this cash those associated with task difficulty (Philiastides & Sajda 2007).

Other types of symmetric fusion approaches use feature extraction techniques from each modality (e.g. EEG power, MVPA fMRI patterns), then directly correlate these features with one another on a trial-by-trial basis. In another elegant example of symmetrical EEG-fMRI fusion, (Griffiths et al. 2019) offered a new perspective on the role of alpha/beta oscillations in the human brain. These rhythms have long been scrutinized for their contribution to cortical idling (Pfurtscheller 2003) and functional inhibition of task irrelevant brain regions (Jensen & Mazaheri 2010, Klimesch et al. 2007). In (Griffiths et al. 2019), the authors offered an alternative account, whereby alpha/beta desynchronization could act as a proxy for information processing, in line with a task-induced reduction in neuronal noise correlations (Haegens et al. 2011).

Participants engaged in an associative memory task where they had to vividly imagine pairing a word (noun) with a previously presented dynamic stimulus (e.g. a video, selected from a larger set of four items). In a separate retrieval task, participants were first presented with the same noun and had to report which video the word was previously paired with. The analysis of the neural data proceeded in a symmetric fashion, whereby the EEG and fMRI data were first analysed independently to produce task-relevant representations that would later enable the fusion.

A searchlight representational similarity analysis (RSA) was carried out on the fMRI data to quantify the level of stimulus-specific information by estimating the difference be-

tween neural patterns of matching vs differing videos. During encoding, significant patterns emerged in visual occipital areas as well as in frontal and temporal clusters known to be involved in high-level conceptualization of the stimulus (Holroyd et al. 2018, Rice et al. 2015). During the retrieval task, neural patterns were compared against those of the encoding task, with stimulus-specific information arising in regions of the fusiform gyrus bilaterally.

EEG analysis was carried out in source space via beamforming techniques (VanVeen et al. 1997). The authors reported significant alpha/beta power decreases (desynchronization) – relative to pre-stimulus baseline – in areas of the occipital lobe during the encoding task. Correspondingly, alpha/beta power decreases were also observed in areas of the ventral visual stream (including the fusiform gyrus), when contrasting recalled and forgotten trials during the retrieval task. Interestingly, these areas largely overlapped with those conveying stimulus-specific information in the fMRI analysis.

Using activity from these areas of overlap, the authors performed trial-wise correlations in alpha/beta power estimates from the EEG and the level of stimulus-specific information (similarity index) from the fMRI, thereby enabling symmetric fusion of the two datasets (Fig. 6). They found a negative relationship between the two measures, suggesting that decreases in alpha/beta power can be thought of as a proxy of information processing. They further confirmed that these power decreases do not carry representational information about the stimulus as such but rather provide favorable conditions (i.e. a low neuronal noise environment) under which the internal representations of relevant stimuli can emerge.

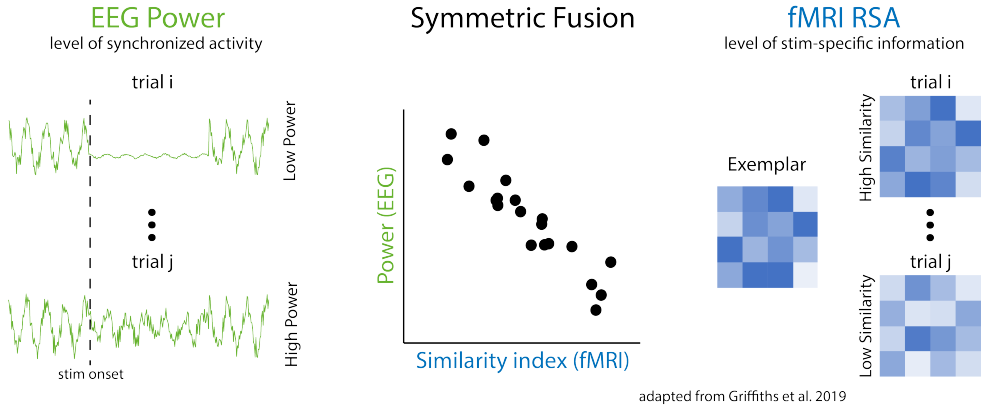

Figure 6

Symmetric EEG-fMRI fusion during an associative memory task (Griffiths et al. 2019). EEG and fMRI data were analyzed separately to quantify power in the alpha/beta frequency bands in the EEG (green) and similarities in multivariate fMRI patterns between matching and differing stimuli (blue), during encoding and retrieval of associative memories. Trial-wise measures from each neuroimaging modality were then correlated directly, revealing that power decreases in the EEG scale with the level of representational similarity reflected in the fMRI.

This example highlights another potential advantage of EEG-fMRI fusion beyond the obvious temporal decoupling of standard fMRI activations maps. Specifically, by relating a functionally meaningful and well recognized electrophysiological phenomenon (i.e. changes in spectral oscillations) to changes in stimulus representations in the functional data, they offered novel insights into the functional architecture of information gating in the human brain.

4. FUTURE DIRECTIONS

4.1. EEG/fMRI at Ultra-High MR fields

Most EEG/fMRI experiments have been done at MR field strengths of 3T or less, though higher field strengths provide spatial resolutions that enable measurements at the laminar scale of the cortex. For example, EEG-fMRI studies at 3T have provided evidence that there are layer specific dependencies of cortical EEG oscillations that may provide insight into laminar specific feedforward and feedback processes (Scheeringa et al. 2016). However ulta-high fields ($\geq$ 7T) enable much better resolution at the mesoscopic (laminar) scale. Though ultra-high field MR systems for human brain imaging are being developed and deployed, an obvious question is whether simultaneous EEG measurements are possible at these higher fields, where inductive pickup, artifacts, and safety due to electrode heating are of greater concern(Jorge et al. 2015b,a). Several groups have been addressing this and developing ultra-high field EEG-fMRI which focus on open coil design and new EEG cap designs that eliminate the classic "pig tail" configurations that act as antennas for electromagnetic pickup (see Figure 7.) Exciting to consider is how this increased spatial resolution of the hemodynanmics, fused with concurrent EEG measures, will yield insight into the meso-scale dynamics of human brain function.

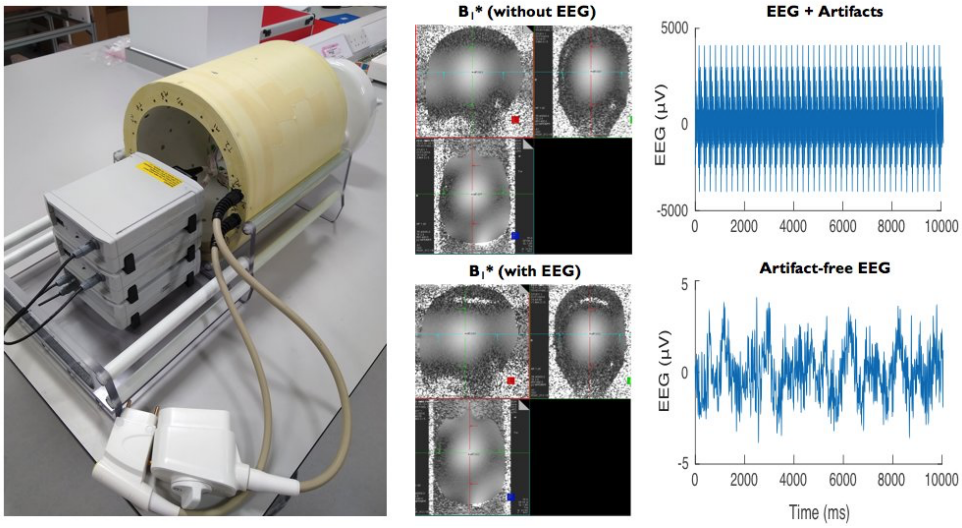

Figure 7

EEG-fMRI system at 7T being developed at The University of Glasgow (Paterson et al. 2020). (left) A picture of the 8-channel transceiver array coil with space provisions to route the cables to the amplifier pack directly behind the coil, which is currently not possible with the most commonly used commercial 7T head coils, (middle) the spatial distribution of the measured B1+ maps recorded on a phantom with and without the EEG caps, (right) EEG data recorded on a phantom before and after gradient artifact removal.

4.2. Targeted Neurostimulation and Perturbation-based Neuroimaging

Optogenetics has revolutionized the study of the nervous system by enabling highly specific control of neural activity in awake, behaving animals (Deisseroth 2011). It has provided

researchers a tool for directly perturbing neural circuits and thus a new pathway for inferring causal relationships between neural activity and behavior. Though an exciting and important tool in the neurosciences, the use of optogenetics is currently limited to animal models.

In humans, direct manipulation of neural activity is usually done via neurostimulation. Non-invasive neurostimulation is largely based on systems that either use transcranial magnetic stimulation (TMS), transcranial electrical stimulation (TES) and more recently, focused ultrasound (FUS). There is increasing interest in developing systems which enable precise targeting of these stimulation modalities. For example, integrated EEG/TMS systems are being used to provide temporal precision and targeting (Miniussi & Thut 2010), namely by triggering the stimulation given the EEG dynamics (Zrenner et al. 2016). Conversely, fMRI/TMS systems focuses on spatial precision (Ruff et al. 2009), the goal to determine which networks and distal sites are affected when stimulation is applied focally. Some groups, including our own, have recently been working to develop integrated EEG/fMRI/TMS systems (Faller et al. 2019, George et al. 2019). One immediate application of these systems is to optimize the targeting for neurostimulation theraputics, for example TMS for the treatment of major depression disorder (MDD). However such an integrated system could also be of general use to human neuroscience researchers given it would enable observation of brain-wide spatio-temporal dynamics following specific stimulation patterns. Ultimately these systems could be designed to be "closed-loop" such that they support active experimental design and adaptive sampling, transition the field to an approach of perturbation-based neuroimaging, where causal inferences between human brain activity and behavior are more directly explored.

4.3. Deep learning Models for Fusion of EEG/fMRI

As the use of EEG/fMRI becomes more prevalent, additional data will be available to utilize for developing sophisticated machine learning models that rely on large datasets. For example, deep learning (Goodfellow et al. 2016) offers an exciting approach to consider when fusing EEG/fMRI. Though deep learning models are often thought of as "blackbox", and difficult to interpret, there are some aspects of these models that are well-matched to the EEG/fMRI fusion problem. For example, convolutional neural networks (CNN) implement temporal and/or spatial convolution operators that are similar in form to the linearized forward models that are typically used to map neural sources to the EEG and fMRI measurement spaces. However CNNs have the advantages of being able to learn non-linear representations –i.e. manifolds – in which to relate the two modalities, thus providing flexibility in the mapping. Our group, for example, has leveraged the idea to build a symmetric fusion system of "neural transcoders" which use CNNs to map from one modality to another by encoding the data into a latent source space and decoding it into the alternative modality (Liu & Sajda 2019). Simulation results show that the approach is able to learn latent source spaces at the temporal resolution of the EEG, but with spatial resolution close to the fMRI, as well as generate one modality from the other given novel test data. Given the continued development of deep learning methods and the likely increase in EEG/fMRI data, additional machine learning developments, as they relate to EEG/fMRI fusion, are likely on the horizon.

SUMMARY POINTS

1. Simultaneous acquired EEG and fMRI (EEG/fMRI) enables mapping of macroscale spatiotemporal dynamics in the human brain.
2. Electromagnetic interaction bewteen the modalities introduces artifacts which affect the signal to noise, reducing data quality relative to acquiring the modalities separately.
3. Critical is exploiting the common variance across the modalities in a away that enables inferences that are not possible via non-simultaneous acquisition.
4. Symmetric and asymmetric data fusion and machine learning methods have been developed that exploit this common variance.
5. Fusion of these simultaneous measures have enabled inferences relating brain activity to behavior that are not otherwise possible when the modalities are acquired separately.
6. Developments in high field MR, targeted neurostimulation, and deep learning all promise to further promote the utility of EEG/fMRI for non-invasively identifying and tracking human brain dynamics.

DISCLOSURE STATEMENT

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