

## Primer

# A M/EEG-fMRI Fusion Primer: Resolving Human Brain Responses in Space and Time

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Any cognitive function is mediated by a network of many cortical sites whose activity is orchestrated through complex temporal dynamics. To understand cognition, we need to identify brain responses simultaneously in space and time. Here we present a technique that does this by linking multivariate response patterns of the human brain recorded with functional magnetic resonance imaging (fMRI) and with magneto- or electroencephalography (M/EEG) based on representational similarity. We present the rationale and current applications of this non-invasive analysis technique, termed M/EEG-fMRI fusion, and discuss its pros and cons. We highlight its wide applicability in cognitive neuroscience and how its openness to further development and extension gives it strong potential for a deeper understanding of cognition in the future.

## Introduction: Identifying Human Brain Responses in Space and Time

We take our cognition for granted: reading these words, recognizing a voice, or remembering where you left your phone are cognitive functions we engage in regularly and effortlessly. The apparent simplicity, however, belies the complexity of the underlying choreography of neural activity. Each cognitive function involves a network of cortical sites with specific temporal dynamics. Some sites exhibit transient signals, quickly transferring information across the network; other sites manifest lingering responses for hundreds of milliseconds. Thus, a key to characterizing how neural activity enables cognitive function is to identify neural activity simultaneously in space and time with high resolution.

This is a major challenge for contemporary cognitive neuroscience because current non-invasive brain measurement techniques excel in spatial or temporal resolution but not in both. Magneto- and electroencephalography (M/EEG) has excellent temporal resolution at the millisecond level but lacks spatial resolution. In contrast, functional magnetic resonance imaging (fMRI) can resolve brain activity-related blood property changes even below the millimeter level but is too sluggish to resolve brain activity at the rapid timescale at which it unfolds. Thus, when considered in isolation, each technique leaves the many-to-many mapping between brain regions and time points underspecified (Figure 1A). However, the complementarity of the techniques' virtues inspired the idea that, by combining the measurement data, one might combine their virtues while overcoming their shortcomings (Dale and Halgren, 2001; Debener et al., 2006; Huster et al., 2012; Jorge et al., 2014; Rosa et al., 2010).

Here we discuss one promising recent manifestation of this idea based on representational similarity that we termed M/EEG-fMRI fusion (Cichy and Teng, 2017; Cichy et al., 2014,

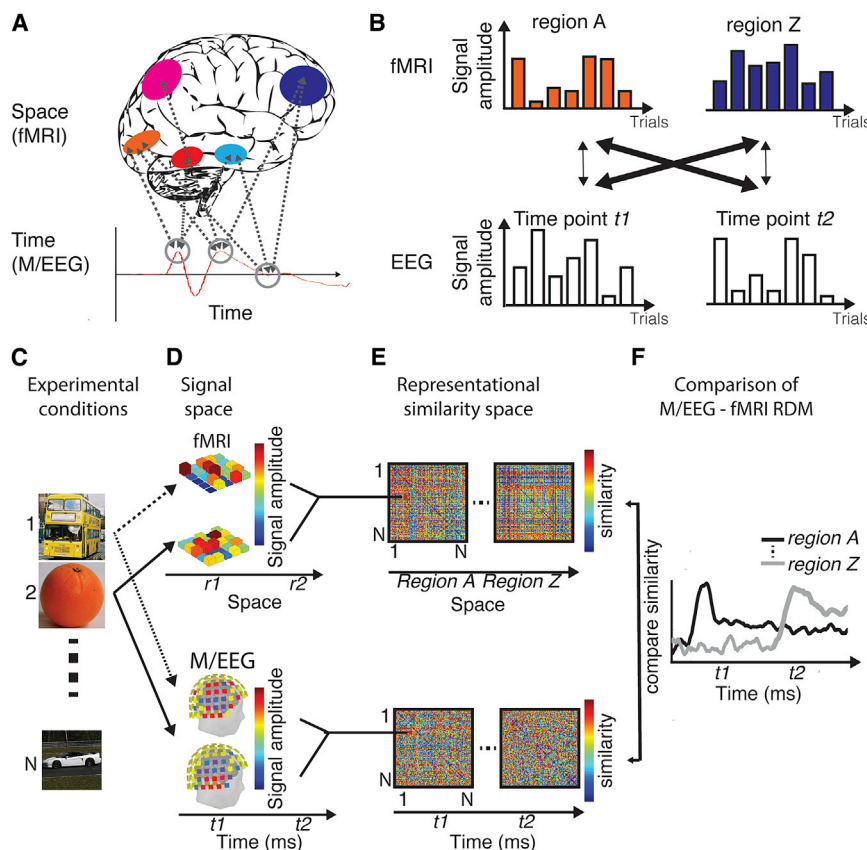
2016). We begin by introducing the technique in its basic formulation and compare it with related approaches. We then highlight recent research using M/EEG-fMRI fusion to shed new light on the neural dynamics of sensory processing and higher-level cognitive functions. We thereby demonstrate the flexibility of the M/EEG fMRI fusion framework for adaptation and development. We close with a discussion of the future potential of M/EEG-fMRI fusion and its limitations. We argue that M/EEG-fMRI fusion will contribute to distilling the best of current imaging method developments that push the limits toward new levels of theoretical description in the human brain.

## The Basic Formulation of M/EEG-fMRI Fusion

How can mapping of neural responses observed at different time points in M/EEG and fMRI activations at different locations be resolved? One idea to forge a link between spatial locations in fMRI and time points in M/EEG is to intentionally introduce additional experimental constraints. For example, researchers have used trial-by-trial variability in simultaneous EEG-fMRI for this purpose (Debener et al., 2006; Figure 1B). The idea is that measurements of neural activity by different imaging modalities reflect the same generators when they correlate on a trial-by-trial basis. In this way, activated brain regions identified with fMRI were linked to neural responses at particular time points measured with M/EEG.

M/EEG-fMRI fusion is similar in that it also uses experimentally induced constraints to link M/EEG and fMRI data (Figures 1C–1F). However, it differs in two fundamental ways. First, it harvests condition-by-condition rather than trial-by-trial variability to link measurements of brain activity in different modalities. This allows combining brain measurements that cannot be taken simultaneously, such as fMRI and magnetoencephalography (MEG). Second, it relates measurements to each other in a multivariate way rather than by relating univariate averages. This is motivated





**Figure 1. Identifying Brain Responses in Space and Time**

(A) Problem formulation. Any cognitive function is underpinned by complex spatiotemporal neural dynamics, with many brain regions contributing to it at many time points. M/EEG and fMRI resolve these dynamics well only in time or space, respectively, leaving the many-to-many mapping between brain regions and time points underspecified.

(B) Single-trial EEG/fMRI. This technique links time points in EEG to brain regions in fMRI by the constraint that signal amplitudes should covary across measurements when they reflect the same neural responses.

(C–E) Mechanics of basic M/EEG/fMRI fusion exemplified for a visual experiment. M/EEG-fusion is best understood as a particular application of RSA.

(C) A sufficiently large condition set (here,  $N$  object images).

(D) Multivariate brain responses to the stimuli are mapped in their respective signal space.

(E) We abstract away from the incommensurate signal space to a common similarity space, calculating pairwise dissimilarities between data for experimental conditions. The results are saved in so-called representational dissimilarity matrices (RDMs), indexed in rows and columns by the  $N$  conditions compared.

(F) In a final step, M/EEG and fMRI RDMs are compared for similarity, specifying the mapping between time points in M/EEG and regions in fMRI by the constraint of representational similarity.

by the idea that signals relate to each other at the level of distributed population codes rather than mass averages (Averbeck et al., 2006; Jacobs et al., 2010; Kriegeskorte and Kreiman, 2011; Panzeri et al., 2015; Stanley, 2013). Further, it may provide higher sensitivity than univariate approaches by pooling signals across measurement channels (Haynes, 2015).

It is easy to see how these ideas can be practically implemented by considering M/EEG-fMRI fusion as a particular case of representational similarity analysis (RSA) (Kriegeskorte et al., 2008a; Kriegeskorte and Kievit, 2013). The goal of RSA is to relate incommensurate multivariate measurement spaces (such as MEG sensor spaces, fMRI voxel spaces, or model unit spaces) by abstracting signals into a common similarity space.

We describe the process step by step and exemplify it by an experiment carried out to investigate visual object processing. First, a set of conditions is chosen that is believed to capture the diversity of neural processing underlying a cognitive function to a sufficient degree (here, a diverse set of objects) (Figure 1C). Then M/EEG and fMRI measurements are made for these conditions (Figure 1D). In each measurement space separately, for all pairwise combinations of conditions, we calculate the similarities (or, equivalently, the dissimilarities) between their multivariate measurements (Figure 1E) in the signal spaces (i.e., voxel activation patterns in fMRI and sensor activation patterns in M/EEG). A multitude of different measures of similarity and dissimilarity are available (Guggenmos et al., 2018; Walther et al., 2016). For demonstration purpose here, and also often also in practice,

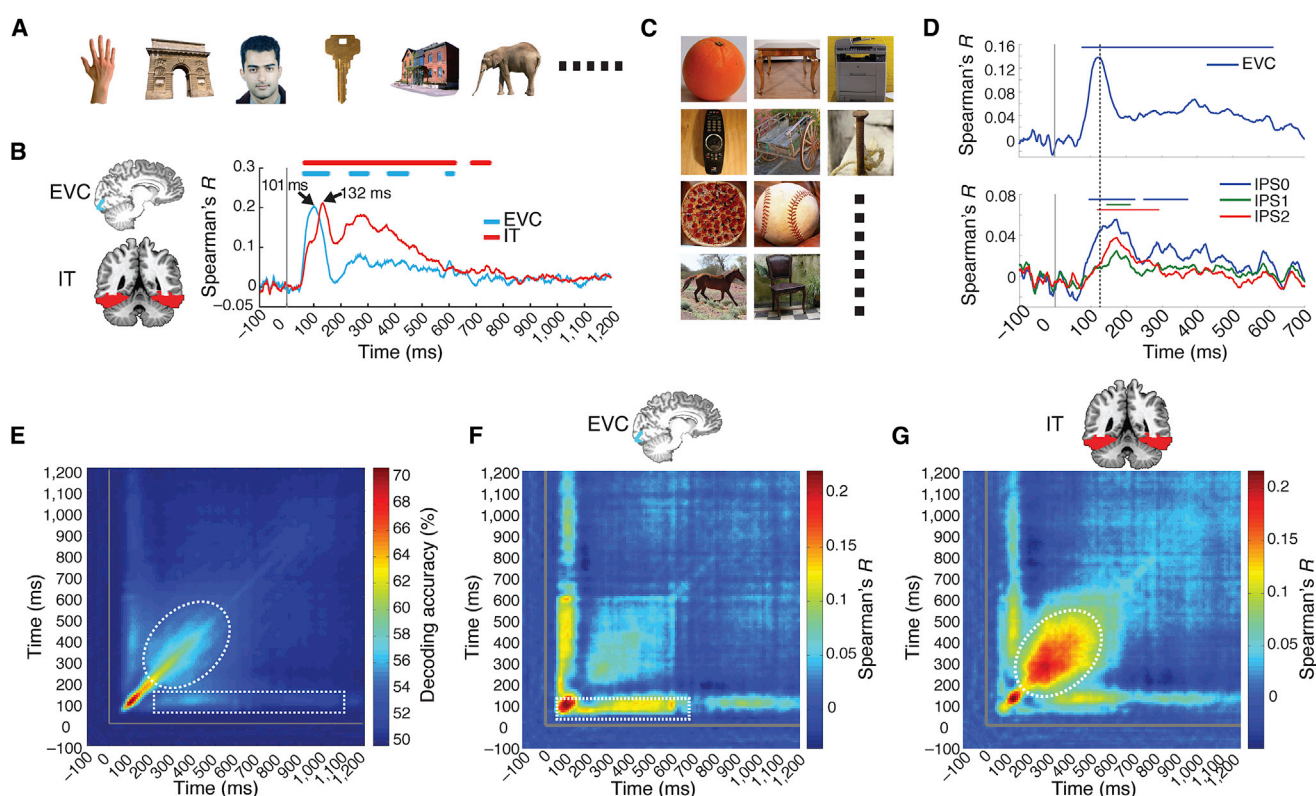
simple correlation (or 1 minus correlation for dissimilarity) can be used. In any case, the resulting values are stored in matrices indexed in rows and columns by the compared conditions, called representational dissimilarity matrices (RDMs). RDMs summarize which conditions elicit similar or dissimilar patterns in regions for fMRI and for time points for M/EEG. Crucially, although RDMs originate from incommensurate source signals, they have the same structure and dimensionality. This makes them directly comparable. Thus, by determining the similarity of RDMs across fMRI and M/EEG measurement spaces, we can test the hypothesis that the same neural generators are measured in particular locations at particular time points (Figure 1F).

In sum, M/EEG and fMRI data can be related to each other (fused) on the basis of common representational structure despite the incommensurate signal source space.

Below, we detail how M/EEG-fMRI fusion was used to reveal spatiotemporal dynamics of cognitive function. We first focus on visual processing.

### The Spatiotemporal Dynamics of Visual Processing

The first application of M/EEG-fMRI fusion investigated the cascade of spatiotemporal processing during visual object processing using a region of interest (ROI) approach (Cichy et al., 2014). Brain responses were recorded with MEG and fMRI while participants viewed a set of 92 images of everyday objects (Figure 2A; stimuli from Kiani et al., 2007; Kriegeskorte et al.,



**Figure 2. Methods, Results, and Variants of ROI-Based M/EEG-fMRI Fusion for Understanding Visual Processing**

(A and C) Participants viewed a set of (A) 92 object silhouette images or (C) 118 object images on real world backgrounds while their brain activity was recorded with MEG and fMRI.

(B and D) M/EEG-fMRI fusion between MEG sensor activation patterns and fMRI BOLD activation patterns in an ROI approach revealed brain responses earlier in the early visual cortex (EVC) than at later stages in the (B) ventral (inferior temporal [IT] cortex) and (D) dorsal stream (intraparietal sulcus 0–2). Colored lines above curves indicate statistically significant effects.

(E) The time generalization method applied to MEG data as recorded for stimuli in (A) revealed a pattern suggesting fast changing, i.e., transient and slow changing, i.e., persistent components (indicated by a dashed white line).

(F and G) Fusion of the M/EEG data analyzed using the temporal generalization method with fMRI revealed that different aspects of persistent neural responses are related to the (F) EVC and (G) IT cortex, respectively.

2008b). Focusing on the ventral visual stream, the authors fused MEG data with fMRI ROI data from the early visual cortex (EVC) and the inferior temporal (IT) region as the starting and end points of the cortical visual processing hierarchy. They found that neural responses in the EVC emerged and peaked earlier than in the IT region (Figure 2B). This result was consistent with the idea of the ventral visual stream as a hierarchical processing cascade (DiCarlo and Cox, 2007; Felleman and Van Essen, 1991) and demonstrated the suitability of the M/EEG-fMRI fusion approach to evaluate patterns of human brain responses in space and time. An independent study using a new set of everyday object images (Figure 2C) replicated the initial finding in the ventral stream and demonstrated a processing cascade in the dorsal stream, providing novel time stamps for brain responses in the parietal cortex (Figure 2D; Cichy et al., 2016; see also Mohsenzadeh et al., 2019).

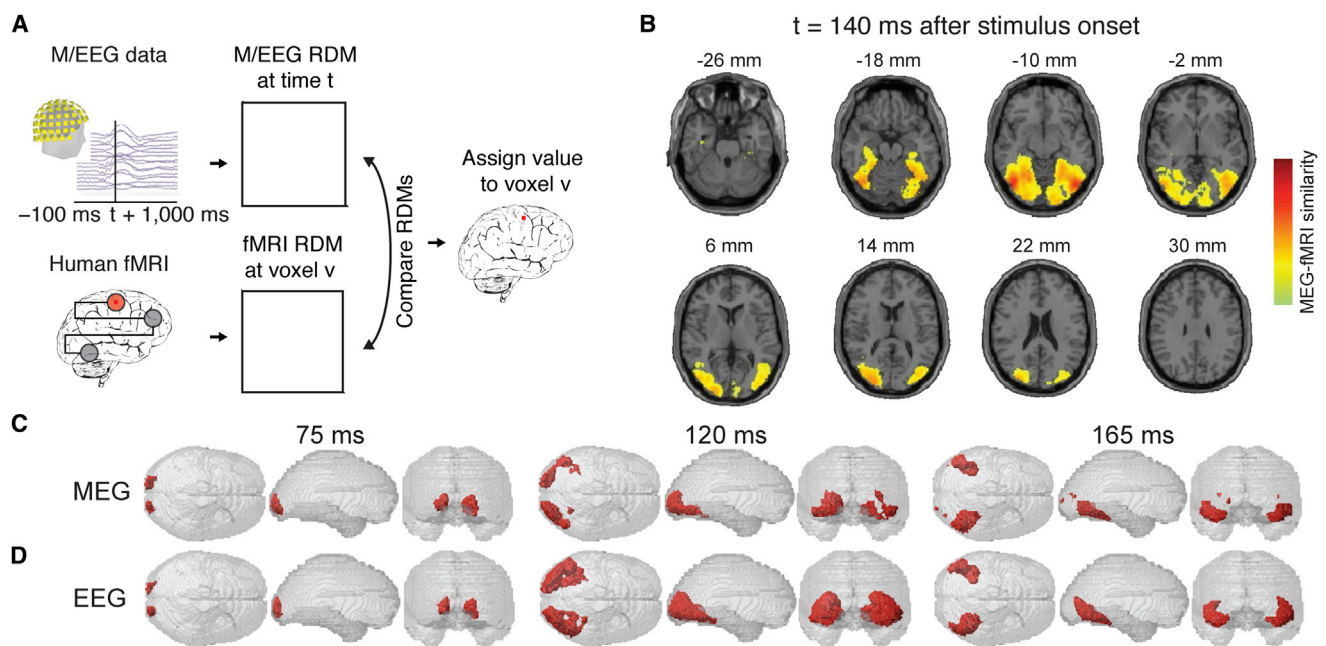
Subsequent research applied M/EEG-fMRI fusion to investigate processing of visual content other than objects. For example, one study investigated the spatiotemporal dynamics underlying face perception (Muukkonen et al., 2020). Fusion of

EEG with fMRI data revealed a processing cascade starting from the EVC and progressing into cortical regions specialized for processing of faces (i.e., face-selective region occipital face area [OFA] and fusiform face area [FFA]) as well as parietal regions. Another study applied M/EEG-fMRI fusion to investigation of scene perception. The authors presented participants with images of scenes of different layout and texture (Henriksson et al., 2019). They found that an area known to be selective to the processing of visual scenes, the occipital place area (OPA), was involved in processing of spatial layout within 100 ms after image presentation. This provided evidence that the OPA is involved in rapid encoding of spatial layout.

M/EEG-fusion is not a single fixed formulation of an algorithmic idea but is best understood as a multivariate analysis framework that can easily be combined with other multivariate data analysis approaches to yield a better description and further theoretical insights. We discuss two major examples that have developed M/EEG-fMRI fusion further in this spirit.

A first essential step was localization of persistent versus transient dynamics by a combination of M/EEG-fMRI fusion with what





**Figure 3. Methods, Results, and Variants of Searchlight-Based M/EEG-fMRI Fusion for Understanding Visual Processing**

(A) M/EEG-fMRI fusion using the volumetric searchlight approach. A MEG RDM is calculated for every time point  $t$ , and a fMRI RDM is calculated for every voxel  $v$  in the brain based on the multivariate activation pattern in its vicinity. The MEG and fMRI RDMs are compared, and the result is noted at the position of the voxel  $v$ . For each time point, this results in a 3D map of representational similarity between M/EEG and fMRI data.

(B) Example of searchlight-based M/EEG-fMRI fusion for 140 ms after onset of an object image.

(C) The searchlight analysis is repeated across time, yielding a video of how human brain responses unfold over time.

(D) Fusion of fMRI data with EEG data yields comparable results as when MEG data are used, as shown in (C).

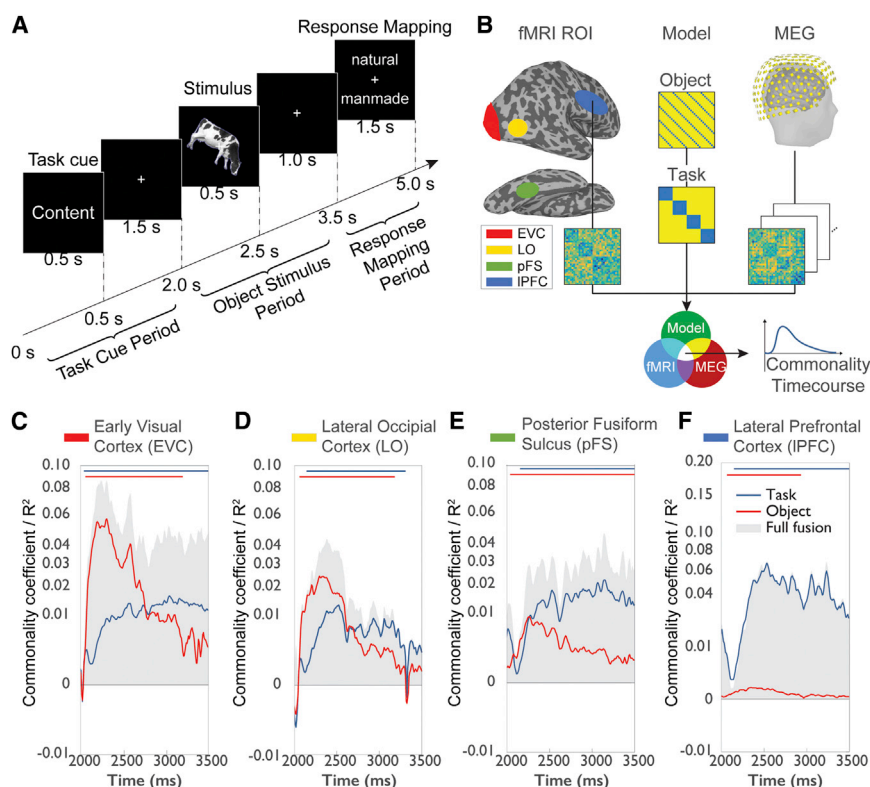
A red color in (C) and (D) indicates significant fusion results.

is now commonly called time generalization analysis (King and Dehaene, 2014). The idea of time generalization is to provide a deeper understanding of neural dynamics by assessing how similar multivariate M/EEG signals are over time. One key distinction is the longevity of representations: if representations change fast over time, then the dynamics are transient; if representations stay the same over time or recur, then the dynamics are persistent. Time generalization analysis typically produces 2-dimensional matrices (indexed in time in both dimensions), indicating when multivariate representational spaces in M/EEG are similar. Algorithmically, this can, for example, be achieved by multivariate pattern classification; a machine learning classifier is trained to distinguish conditions based on data from one time point and is then tested on data from all other time points (Cichy et al., 2014; Isik et al., 2014; King et al., 2014; Meyers et al., 2008). Above-chance classification results at time point combinations other than identical for training and testing data indicate similar neural patterns across time and, thus, suggests persistent dynamics. Conducted in this manner, time generalization analysis on MEG data recorded during object perception showed a complex pattern of fast transient (e.g., high decoding accuracy early along the diagonal) and persistent representations (Cichy et al., 2014; Figure 2E, indicated by white dotted shapes). The presence of several persistent components immediately posed the question from where in the brain they stem. M/EEG-fMRI fusion provided the answer by localizing these persistent representations to the EVC and IT region (Figures 2F and 2G). This result provided

a description of the spatiotemporal neural dynamics during vision with respect to the theoretical distinction between transient and persistent brain responses.

A second essential step was extension to a spatially unbiased analysis using the searchlight approach (Figure 3A). There, instead of focusing on a predefined set of regions, representational correspondence to M/EEG is established for every fMRI voxel independently based on the blood oxygenation level dependent (BOLD) activation pattern in its local vicinity. In detail, conducted for each particular time point of M/EEG data, this results in a spatially unbiased map of where fMRI activation patterns in the brain are representationally similar to EEG data of that time point. Taking the maps for all time points together results in a temporally resolved video of how neural responses evolve spatially. For object processing, spatially unbiased searchlight-based fusion of fMRI and MEG data replicated and extended the ROI-based result to a finer-grained view of how neuronal responses evolved during perception in the human brain (Figures 3B and 3C; Cichy et al., 2016).

M/EEG-fMRI fusion can, in principle, be used with MEG, EEG, or a combination (Figure 3D; Cichy and Pantazis, 2017). The usability with EEG makes M/EEG-fMRI fusion a versatile analytical tool that is well accessible in a large number of sites in the world. However, MEG and EEG do have differential sensitivities to neural signals (Hämäläinen et al., 1988). This is mirrored in the fusion results of fMRI, with MEG or EEG capturing unique aspects of neural representations (Cichy and Pantazis, 2017). In effect,



**Figure 4. Applications and Extensions of M/EEG Fusion to Processing Task Context**

(A) Experimental paradigm. In each trial, participants first receive a task cue on which task to carry out (e.g., judge whether the upcoming object is natural or manmade). Later, they are presented a stimulus probe. Last, they give their response (Hebart et al., 2018).

(B) Content-specific formulation of M/EEG-fMRI fusion. In addition to constructing RDMs based on region-specific fMRI BOLD activation and time-resolved MEG data, model RDMs are created, capturing the effect of different aspects of the data, such as the task or object. For example, in the task model RDM condition combinations belonging to the same task were given the value 0 (to code similarity; here, a blue color) or 1 otherwise (i.e., to code dissimilarity; here, a yellow color). The three types of RDMs are then combined using commonality analysis to reveal the aspects of the data uniquely related to each model (Hebart et al., 2018).

(C–F) The results of content-specific fusion focusing on the object stimulus period from 2.0–3.5 s for (C) the EVC, (D) lateral occipital cortex, (E) posterior fusiform sulcus, and (F) lateral prefrontal cortex revealed a parallel rise in task-related signals throughout cortex, with an increasing dominance of task over object representations along the processing hierarchy (Hebart et al., 2018). Gray shaded areas indicate total variance explainable by M/EEG-fMRI fusion. Red and blue lines above curves indicate significant effects.

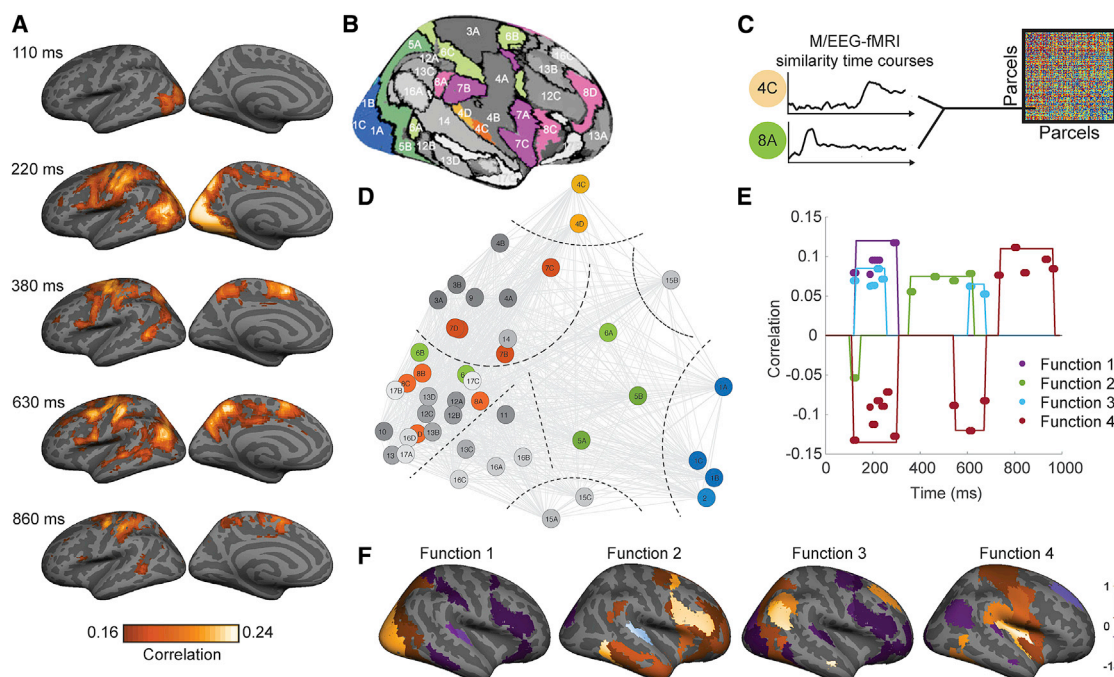
whether to acquire MEG or EEG for fusion might depend on the exact experimental goals. For example, for fusion with high-frequency oscillations, MEG might be more suited because of its relatively better ability to resolve these signals. In contrast, for fusion with very deep sources, EEG might be more appropriate because magnetic fields decay strongly with distance to the sensors. The differences in sensitivity of MEG and EEG to different aspects of neural activity also imply that fusion of fMRI data with MEG and EEG combined has the best potential to yield the most refined view of human brain activity.

Together, these studies in visual processing demonstrate the feasibility, versatility, and potential of M/EEG-fMRI fusion to shed new light on the spatiotemporal processing underlying cognitive processing. The fact that similar spatiotemporal processing cascades were observed in the visual system for different content and in independent studies speaks qualitatively for the ability of the technique to yield reproducible and reliable results. This was also ascertained quantitatively by comparing the results of M/EEG-fMRI fusion across data and stimulus sets, suggesting good generalizability and reliability (Mohsenzadeh et al., 2019).

### The Spatiotemporal Dynamics of Higher-Level Cognition

Although M/EEG fMRI fusion was first established in the field of perception, it is in no way limited to this aspect of cognition. Here we highlight two studies that applied M/EEG-fMRI fusion to higher-level cognition and show how the technique was developed further in each case to reach the desired theoretical insights.

The first example is a study investigating how humans process the task contexts in which objects occur (Hebart et al., 2018; Figure 4A). Tasks and behavioral goals strongly influence how we perceive the world. Their large effect on perception is mirrored in the finding that tasks are processed in many different regions of the brain and influence visual processing (Bracci et al., 2017; Erez and Duncan, 2015; Harel et al., 2014; Vaziri-Pashkam and Xu, 2017). This raises the question how activity in these brain regions is modulated by tasks across time. Hebart et al. (2018) used M/EEG-fMRI fusion to shed light on this issue. In each trial, participants were first given one of four tasks (i.e., judge an object's animacy, size, the color of the outline, or tilt). Then an object from a set of different categories (e.g., cows, flowers, or trees) was presented on which participants had to carry out the task, followed by a delayed response screen. The authors focused their analysis on the object presentation period and asked with which spatiotemporal dynamics neural processing of task and of object emerged independently. This posed a challenge for the basic formulation of M/EEG-fMRI fusion; processing of task and object are concurrent, whereas M/EEG-fMRI fusion in its basic formulation does not differentiate between different aspects of processing. As a solution, the authors used commonality analysis (also known as variance partitioning; Seibold and McPhee, 1979). They formulated, in model RDMs, the effect of task and object category and then determined separately for each of the two model RDMs the proportion of variance shared between MEG and fMRI (Figure 4B). The results (Figures 4C–4F) revealed a parallel rise in task-related signals throughout the cortex, with an increasing dominance of task over object



**Figure 5. Applications and Extensions of M/EEG Fusion to Attentional Processing**

(A) Results of M/EEG-fMRI fusion investigating the spatiotemporal dynamics of sensory processing under different states of attention (here for the left hemisphere) (Salmela et al., 2018).

(B) Based on a brain parcellation atlas, M/EEG fMRI time courses were defined.

(C) The time courses were compared for similarity and stored in a timecourse similarity RDM.

(D) Visual inspection revealed several clusters in the similarity relations of the timecourse similarity RDM.

(E and F) Discriminative analysis was carried out on the clustered data, and the coefficients of the four discriminative functions were plotted across (E) time and (F) space (Salmela et al., 2018). This revealed larger-scale networks of brain responses across space and time, reminiscent of sensory processing (function 1), top-down guided attentional control (function 2), brain state transitions (function 3), and response control (function 4). Colors indicate coefficient values for the discriminative functions.

representations from early to higher visual areas and further to the frontal cortex. This nuanced spatiotemporal description has theoretical effects on several grounds. First, it demonstrated that task information is communicated rapidly between brain regions involved in task processing (Siegel et al., 2015). Further, it speaks against the idea of the visual cortex having a passive role in visual processing from which the task-malleable frontal cortex reads out information (Freedman et al., 2003). Instead, it suggests that a task biases visual processing in the occipital cortex with increasing strength along the visual processing hierarchy.

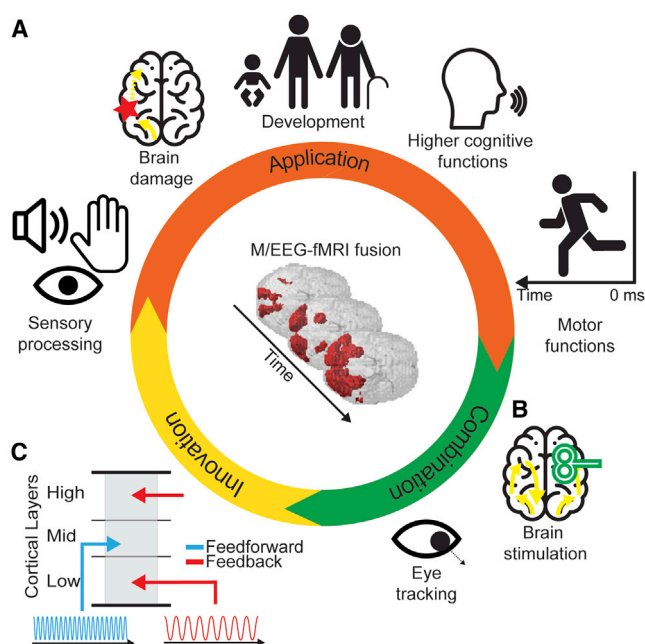
Commonality analysis as used by Hebart et al. (2018) is an elegant way to add constraints to M/EEG-fMRI fusion to make it content specific. However, it is not the only one. Another possibility is to use conjunction inference (Nichols et al., 2005). Instead of calculating shared variances, the idea is to use a logical “and” operation; that is, to count only those locations and time points related to processing of a particular content that also significantly relate to a model RDM of the content (Khaligh-Razavi et al., 2018). The choice between different ways to make M/EEG-fMRI fusion content specific is best determined by theoretical considerations regarding in what kind of effect the investigator is interested.

The second example is a study investigating the spatiotemporal neural dynamics related to attentional processing (Salmela

et al., 2018). A large body of work has identified brain networks that underlie different components of attention and has described the temporal dynamics with which attention is being processed. However, the relationship between the spatially localized networks and the complex temporal dynamics is less well understood. Therefore, Salmela et al. (2018) used M/EEG-fMRI fusion to investigate the many-to-many mapping between brain regions and processing stages of attention. In the experiment, participants performed visual and auditory tasks (orientation or pitch one-back discrimination) separately or simultaneously and with or without distractors while EEG and fMRI data were recorded. The set of different combinations of experimental factors influencing attention was the level at which the data were analyzed further.

In the first step, the authors fused the EEG with fMRI data, revealing a processing cascade from sensory to parietal regions and further into frontal regions (Figure 5A). In the second step, the authors took M/EEG-fMRI analysis up one level by making its results the starting point for further analysis. After conducting M/EEG-fMRI fusion based on cortical parcels (Figure 5B), they compared the parcel-specific M/EEG-fMRI time courses for similarity (Figure 5C). Visual inspection of the similarity relations between the parcel-specific EEG-fMRI time courses suggested 8 clusters (Figure 5D), which were used for a discrimination





**Figure 6. Future Potential of M/EEG-fMRI Fusion**

(A) M/EEG fMRI fusion may be applied in any field in which M/EEG and fMRI are already applied in isolation.

(B) M/EEG fMRI fusion may be combined with brain stimulation to reveal its effects and to establish causal relationships between neural responses and behavior.

(C) Innovation in M/EEG and fMRI research can be directly harvested by fMRI fusion to reveal novel aspects of neural processing. For example, feedforward and feedback information flow are associated with neural responses in distinct cortical layers and in distinct frequency bands. Thus, fusing M/EEG data resolved in different frequency bands with fMRI data resolved in cortical depth may reveal feedforward and feedback information flow in the brain.

analysis. Four discriminative functions explained 95% of the variance across areas. Their coefficients are plotted in Figure 5E across time and in Figure 5F across space. The functions reveal a large-scale pattern of spatiotemporal dynamics across networks that the authors interpret as four different spatiotemporal components of attention. These results provide new insight into the large-scale spatiotemporal dynamics of attentional processing and are a stepping stone for developing a quantitative spatiotemporal model of attentional processing in the human brain.

In sum, these studies exemplify how M/EEG-fMRI can be used to study complex cognitive phenomena such as task processing and attentional control. They further demonstrate how M/EEG-fMRI fusion can be extended methodologically for deeper theoretical insight by making it content specific or making its results the subject of further analysis.

### Future Potential of M/EEG-fMRI Fusion

As demonstrated above, M/EEG-fMRI fusion is not a particular fixed single-purpose algorithm but, rather, a general and easily extendable analytical framework. This gives M/EEG-fMRI fusion strong potential for future studies of cognitive function in a wide range of domains. We emphasize three different general directions below and provide concrete examples for each.

First, M/EEG fMRI fusion can be used immediately in any domain of investigation in which M/EEG and fMRI are currently employed. Its potential application thus ranges from understanding basic sensory encoding, such as touch or sound (Lowe et al., 2020), to complex cognitive processes (e.g., working memory, language, or planning) and studies of how neural dynamics change in a clinical context (e.g., stroke or mental disease) or during development (e.g., through longitudinal or age-comparative studies) (Figure 6A). To make this more concrete, let us consider three examples. First, M/EEG-fMRI could contribute to a better understanding of how information exchange is coordinated in cognitive functions that have several stages mapping on potentially different brain regions, such as encoding, maintenance, and retrieval in working memory. Another example would be study of the motor system; in particular, the neural activity leading up to a movement. For this, M/EEG fusion would be conducted not forward in time, as, for example, after presentation of a stimulus, but backward in time, locked to the onset of movement. An exciting prospect is that if the results of M/EEG-fMRI time locked to stimulus onset and time-locked to response are combined, then this reveals the full cascade of neural processing between the presentation of a stimulus and the behavioral response. Finally, M/EEG-fMRI fusion could be used in clinical neuroscience to identify how brain damage or mental disease affects information flow, revealing spatiotemporal functional biomarkers to aid with diagnosing disorders or pinpointing impairments as a precursor to therapeutic interventions.

Second, M/EEG-fMRI fusion could be combined with other techniques that already have separate applications in M/EEG and fMRI research. This includes invasive and non-invasive brain stimulation as well as assessment of eye movement and physiological measures. For example, the effect of stimulation, such as transcranial magnetic stimulation (Hallett, 2007; Walsh and Cowey, 2000), to a particular brain region could be assessed in terms of its effect on spatiotemporal network dynamics (Figure 6B). This might help to establish causal relationships between spatiotemporally identified neural responses and cognitive function.

Third, M/EEG-fMRI fusion can immediately benefit from innovation in the techniques involved to provide novel solutions for resolving brain responses. As an example, let us consider the challenge of dissociating information flow in its two fundamental streams: feedforward and feedback. This is a challenging problem for current human neuroimaging because input and output signals overlap at the level where we can measure them noninvasively. Current applications of M/EEG-fMRI fusion to this problem thus use well-proven experimental interventions, such as masking, to dissociate feedforward from feedback information flow (Mohsenzadeh et al., 2018). A further emerging possibility is making use of method innovation (Figure 6C). In space, ultra-high-field fMRI can resolve signals at different cortical depths (Huber et al., 2017; Kok et al., 2016; Muckli et al., 2015). Cortical layers at different depths are differentially targeted by feedforward and feedback anatomical connections (Gilbert, 1983; Larkum, 2013; Markov et al., 2014); thus, differentiating layer-specific activity may help to dissociate feedforward- and feedback-related signaling. In time, feedforward and feedback

information flow are associated with different frequencies. Lower frequencies are more strongly related to feedback and higher frequencies more strongly to feedforward activity (Bastos et al., 2015; Buffalo et al., 2011; van Kerkoerle et al., 2014; Maier et al., 2010; Michalareas et al., 2016). Thus, by fusing layer-specific fMRI and frequency-resolved M/EEG data, it might be possible to directly track feedback and feedforward information flow simultaneously in space and time. This idea also receives support from previous studies that used multivariate methods on time-frequency-resolved data, revealing the kind of fine-grained information necessary for M/EEG-fMRI fusion (Pantazis et al., 2018), and fusion of time-frequency-resolved MEG with fMRI at standard resolution (Reddy et al., 2017).

In sum, M/EEG-fMRI may prove to be a valuable tool to understand neural dynamics in a wide range of fields of inquiry in its current formulation, in novel combination with other techniques to manipulate brain data, and in epitomizing on innovation for unprecedented analytical power.

### Limitations of the Technique

M/EEG-fMRI fusion is subject to limitations dictated by principle or by its current implementation. We discuss the most important limitations of both kinds below.

A fundamental limitation of M/EEG-fMRI fusion is that it can only reveal aspects of neural activity to which both imaging modalities are sensitive. Thus, inspection of M/EEG or fMRI signals alone will likely reveal more signal in the temporal and spatial domain than when M/EEG and fMRI are combined with fusion. Further, M/EEG-fMRI fusion requires stronger signal-to-noise ratios compared with the results of each technique being considered in isolation to yield significant results because it adds an analysis step that combines two noisy measurements and, thus, noise. The flip side of the coin is that confidence in scientific findings increases with the amount of reasonable constraints the data fulfill. For positive results of M/EEG-fMRI fusion, the representational structure must be similar in both M/EEG and fMRI; this arguably provides a stronger basis to believe the results of fusion to reflect neural activity than when either technique is considered in isolation. Thus, although alternative explanations can never be fully ruled out, M/EEG fMRI fusion results provide a good basis for theoretical inference about neural activity.

A second general limitation is that the power of the M/EEG-fMRI fusion approach depends on the richness of the condition set. When only a few conditions can be defined, the constraints of representational similarity between M/EEG and fMRI data will be low; thus, the established link between spatial and temporal domains will be weak. In contrast, when many experimental conditions are used that capture neural processing underlying a particular cognitive function in a sufficiently diverse manner, the link will be strong. However, the exact number of conditions is not easily established because they interact with multiple factors, including the actual spatiotemporal dynamics to be resolved, the signal-to-noise ratio, and the exact theoretical question.

A third fundamental limitation is that the results can be ambiguous; if two regions share a similar representational format but are activated at different time points, then we cannot ascribe

unique representational dynamics to each. However, this case is unlikely because information traveling between brain regions is transformed in a complex and non-linear manner, in effect also changing the representational format. To further mitigate this concern, the stimulus set could be chosen to maximally disambiguate between ROIs based on previous knowledge of their representational format.

A particular limitation of the current implementation of M/EEG-fMRI fusion is that it considers information about timing based only on M/EEG and information about space based only on fMRI. This is motivated by the idea to combine only aspects across techniques at which each technique excels. However, this might not be the optimal procedure for many experimental settings. Considering temporal information from fMRI might be beneficial when faster-than-usual acquisition is employed (Ekman et al., 2017; Lewis et al., 2016; Poser and Setsompop, 2018), when the cognitive processes in question have dynamics that are slow enough to be captured meaningfully with a sampling rate of seconds, or when experimental interventions are used to draw out cognitive processing in time that otherwise would be rapid. Similarly, spatial information from M/EEG can be considered based on any of the multiple techniques developed to project source space information into the signal space of the brain. Then, fMRI data in a particular location would be related to activity measured in MEG localized to that location. This might, for example, be useful to mitigate the ambiguity in MEG/fMRI fusion when two regions have similar representational formats by assigning unique MEG signals to each based on spatial information in the MEG data.

A limitation of the actual use of M/EEG-fMRI fusion is that the fused data were from separate rather than simultaneous recordings. Although this is currently unavoidable for the combination of MEG and fMRI, nothing prohibits recording EEG and fMRI data simultaneously for fusion. Whether EEG-fMRI fusion works better with data recorded simultaneously or separately is an open question that requires investigation, and this will also likely depend on how much weight the experimenter puts on the respective advantages and disadvantages of each approach. An argument for separate recordings is that the experimental design can be optimized to the specifics of the technique; e.g., not being limited by the sluggishness of the BOLD response, experimental trials may be much more tightly spaced during EEG recordings, increase the signal-to-noise ratio of the EEG data, and, thus, help fusion. Further, separate recordings are easier done in that combining fMRI and EEG requires specialized setups and equipment, creates interactions between the measurements that may affect data quality, and requires additional preprocessing steps. However, simultaneous recordings have unique benefits, too. Brain data are acquired under the exact same conditions (e.g., the exact same sensory stimulation and the same psychological and physiological state of the participant). In contrast, data acquired separately are subsequently subject to variation (e.g., not perfectly matched stimulation conditions, different body postures, or different history of exposure to the same experimental conditions). Thus, arguably, simultaneous recordings reduce unwanted variability compared with separate recordings and might therefore benefit fusion. Simultaneous recordings also suggest a novel direction of method



development. Can fusion using uni- and multivariate approaches based on trial-by-trial variability (Eichele and Calhoun, 2010; Debener et al., 2006; Eichele and Calhoun, 2010) be combined with fusion based on condition-by-condition variability, as discussed here, to yield a more refined view of spatiotemporal dynamics than either fusion would in isolation?

In sum, M/EEG-fMRI fusion is subject to several fundamental and practical constraints that define its general applicability. As any technique, it sheds light on human brain function from a particular perspective only. However, from that perspective, it contributes unique views of human brain function. This does not make any other analytical or measurement technique superfluous. Instead, we believe it is best viewed as an addition to the set of exciting tools of cognitive neuroscience, helping to accrue evidence for theories in the absence of access to ground truth.

## Conclusions

To understand complex neural processing in the human brain, we need to resolve its component processes in space and time at the level where they occur. In the absence of a single non-invasive technique that excels at spatial and temporal resolution, analytical approaches that combine information from several techniques are key. M/EEG-fMRI fusion is such an approach. Its feasibility has been demonstrated in the study of visual perception and has been transferred successfully to the study of higher cognitive functions. It is particularly flexible to extension and well suited to immediately benefit from future developments in the imaging techniques it combines. We thus believe that it has the potential to be fruitfully applied in a wide range of fields to reveal the spatiotemporal dynamics of human cognitive function.

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## REFERENCES

- Averbeck, B.B., Latham, P.E., and Pouget, A. (2006). Neural correlations, population coding and computation. *Nat. Rev. Neurosci.* 7, 358–366.
- Bastos, A.M., Vezoli, J., Bosman, C.A., Schoffelen, J.-M., Oostenveld, R., Dowdall, J.R., De Weerd, P., Kennedy, H., and Fries, P. (2015). Visual areas exert feedforward and feedback influences through distinct frequency channels. *Neuron* 85, 390–401.
- Bracci, S., Daniels, N., and Op de Beeck, H. (2017). Task Context Overrides Object- and Category-Related Representational Content in the Human Parietal Cortex. *Cereb. Cortex* 27, 310–321.
- Buffalo, E.A., Fries, P., Landman, R., Buschman, T.J., and Desimone, R. (2011). Laminar differences in gamma and alpha coherence in the ventral stream. *Proc. Natl. Acad. Sci. USA* 108, 11262–11267.
- Cichy, R.M., and Pantazis, D. (2017). Multivariate pattern analysis of MEG and EEG: A comparison of representational structure in time and space. *Neuroimage* 158, 441–454.
- Cichy, R.M., and Teng, S. (2017). Resolving the neural dynamics of visual and auditory scene processing in the human brain: a methodological approach. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 372, 20160108.
- Cichy, R.M., Pantazis, D., and Oliva, A. (2014). Resolving human object recognition in space and time. *Nat. Neurosci.* 17, 455–462.
- Cichy, R.M., Pantazis, D., and Oliva, A. (2016). Similarity-Based Fusion of MEG and fMRI Reveals Spatio-Temporal Dynamics in Human Cortex During Visual Object Recognition. *Cereb. Cortex* 26, 3563–3579.
- Dale, A.M., and Halgren, E. (2001). Spatiotemporal mapping of brain activity by integration of multiple imaging modalities. *Curr. Opin. Neurobiol.* 11, 202–208.
- Debener, S., Ullsperger, M., Siegel, M., and Engel, A.K. (2006). Single-trial EEG-fMRI reveals the dynamics of cognitive function. *Trends Cogn. Sci.* 10, 558–563.
- DiCarlo, J.J., and Cox, D.D. (2007). Untangling invariant object recognition. *Trends Cogn. Sci.* 11, 333–341.
- Eichele, T., and Calhoun, V.D. (2010). Parallel EEG-fMRI ICA Decomposition. In *Simultaneous EEG and fMRI: Recording, Analysis and Application*, M. Ullsperger and S. Debener, eds. (Oxford University Press), pp. 175–194.
- Ekman, M., Kok, P., and de Lange, F.P. (2017). Time-compressed preplay of anticipated events in human primary visual cortex. *Nat. Commun.* 8, 15276.
- Erez, Y., and Duncan, J. (2015). Discrimination of Visual Categories Based on Behavioral Relevance in Widespread Regions of Frontoparietal Cortex. *J. Neurosci.* 35, 12383–12393.
- Felleman, D.J., and Van Essen, D.C. (1991). Distributed hierarchical processing in the primate cerebral cortex. *Cereb. Cortex* 1, 1–47.
- Freedman, D.J., Riesenhuber, M., Poggio, T., and Miller, E.K. (2003). A Comparison of Primate Prefrontal and Inferior Temporal Cortices during Visual Categorization. *J. Neurosci.* 23, 5235–5246.
- Gilbert, C.D. (1983). Microcircuitry of the visual cortex. *Annu. Rev. Neurosci.* 6, 217–247.
- Guggenmos, M., Sterzer, P., and Cichy, R.M. (2018). Multivariate pattern analysis for MEG: A comparison of dissimilarity measures. *Neuroimage* 173, 434–447.
- Hallett, M. (2007). Transcranial magnetic stimulation: a primer. *Neuron* 55, 187–199.
- Hämäläinen, M.S., Ilmoniemi, R.J., and Sarvas, J. (1988). Interdependence of information conveyed by the magnetoencephalogram and the electroencephalogram. *Theory and Applications of Inverse Problems* (Longman), pp. 27–37.
- Harel, A., Kravitz, D.J., and Baker, C.I. (2014). Task context impacts visual object processing differentially across the cortex. *Proc. Natl. Acad. Sci. USA* 111, E962–E971.
- Haynes, J.-D. (2015). A Primer on Pattern-Based Approaches to fMRI: Principles, Pitfalls, and Perspectives. *Neuron* 87, 257–270.
- Hebart, M.N., Bankson, B.B., Harel, A., Baker, C.I., and Cichy, R.M. (2018). The representational dynamics of task and object processing in humans. *eLife* 7, e32816.
- Henriksson, L., Mur, M., and Kriegeskorte, N. (2019). Rapid Invariant Encoding of Scene Layout in Human OPA. *Neuron* 103, 161–171.e3.
- Huber, L., Handwerker, D.A., Jangraw, D.C., Chen, G., Hall, A., Stüber, C., Gonzalez-Castillo, J., Ivanov, D., Marrett, S., Guidi, M., et al. (2017). High-Resolution CBV-fMRI Allows Mapping of Laminar Activity and Connectivity of Cortical Input and Output in Human M1. *Neuron* 96, 1253–1263.e7.
- Huster, R.J., Debener, S., Eichele, T., and Herrmann, C.S. (2012). Methods for simultaneous EEG-fMRI: an introductory review. *J. Neurosci.* 32, 6053–6060.
- Isik, L., Meyers, E.M., Leibo, J.Z., and Poggio, T. (2014). The dynamics of invariant object recognition in the human visual system. *J. Neurophysiol.* 111, 91–102.
- Jacobs, J., Kahana, M.J., Ekstrom, A.D., Mollison, M.V., and Fried, I. (2010). A sense of direction in human entorhinal cortex. *Proc. Natl. Acad. Sci. USA* 107, 6487–6492.
- Jorge, J., van der Zwaag, W., and Figueiredo, P. (2014). EEG-fMRI integration for the study of human brain function. *Neuroimage* 102, 24–34.

- Khaligh-Razavi, S.-M., Cichy, R.M., Pantazis, D., and Oliva, A. (2018). Tracking the Spatiotemporal Neural Dynamics of Real-world Object Size and Animacy in the Human Brain. *J. Cogn. Neurosci.* **30**, 1559–1576.
- Kiani, R., Esteky, H., Mirpour, K., and Tanaka, K. (2007). Object category structure in response patterns of neuronal population in monkey inferior temporal cortex. *J. Neurophysiol.* **97**, 4296–4309.
- King, J.-R., and Dehaene, S. (2014). Characterizing the dynamics of mental representations: the temporal generalization method. *Trends Cogn. Sci.* **18**, 203–210.
- King, J.-R., Gramfort, A., Schurger, A., Naccache, L., and Dehaene, S. (2014). Two distinct dynamic modes subserve the detection of unexpected sounds. *PLoS ONE* **9**, e85791.
- Kok, P., Bains, L.J., van Mourik, T., Norris, D.G., and de Lange, F.P. (2016). Selective Activation of the Deep Layers of the Human Primary Visual Cortex by Top-Down Feedback. *Curr. Biol.* **26**, 371–376.
- Kriegeskorte, N., and Kievit, R.A. (2013). Representational geometry: integrating cognition, computation, and the brain. *Trends Cogn. Sci.* **17**, 401–412.
- Kriegeskorte, N., and Kreiman, G. (2011). Visual Population Codes: Toward a Common Multivariate Framework for Cell Recording and Functional Imaging (The MIT Press).
- Kriegeskorte, N., Mur, M., and Bandettini, P. (2008a). Representational similarity analysis - connecting the branches of systems neuroscience. *Front. Syst. Neurosci.* **2**, 4.
- Kriegeskorte, N., Mur, M., Ruff, D.A., Kiani, R., Bodurka, J., Esteky, H., Tanaka, K., and Bandettini, P.A. (2008b). Matching categorical object representations in inferior temporal cortex of man and monkey. *Neuron* **60**, 1126–1141.
- Larkum, M. (2013). A cellular mechanism for cortical associations: an organizing principle for the cerebral cortex. *Trends Neurosci.* **36**, 141–151.
- Lewis, L.D., Setsompop, K., Rosen, B.R., and Polimeni, J.R. (2016). Fast fMRI can detect oscillatory neural activity in humans. *Proc. Natl. Acad. Sci. USA* **113**, E6679–E6685.
- Lowe, M.X., Mohsenzadeh, Y., Lahner, B., Charest, I., Oliva, A., and Teng, S. (2020). Spatiotemporal Dynamics of Sound Representations reveal a Hierarchical Progression of Category Selectivity. *bioRxiv*. <https://doi.org/10.1101/2020.06.12.149120>.
- Maier, A., Adams, G.K., Aura, C., and Leopold, D.A. (2010). Distinct superficial and deep laminar domains of activity in the visual cortex during rest and stimulation. *Front. Syst. Neurosci.* **4**, 31.
- Markov, N.T., Vezoli, J., Chameau, P., Falchier, A., Quilodran, R., Huissoud, C., Lamy, C., Misery, P., Giroud, P., Ullman, S., et al. (2014). Anatomy of hierarchy: feedforward and feedback pathways in macaque visual cortex. *J. Comp. Neurol.* **522**, 225–259.
- Meyers, E.M., Freedman, D.J., Kreiman, G., Miller, E.K., and Poggio, T. (2008). Dynamic population coding of category information in inferior temporal and prefrontal cortex. *J. Neurophysiol.* **100**, 1407–1419.
- Michalareas, G., Vezoli, J., van Pelt, S., Schoffelen, J.-M., Kennedy, H., and Fries, P. (2016). Alpha-Beta and Gamma Rhythms Subserve Feedback and Feedforward Influences among Human Visual Cortical Areas. *Neuron* **89**, 384–397.
- Mohsenzadeh, Y., Qin, S., Cichy, R.M., and Pantazis, D. (2018). Ultra-Rapid serial visual presentation reveals dynamics of feedforward and feedback processes in the ventral visual pathway. *eLife* **7**, e36329.
- Mohsenzadeh, Y., Mullin, C., Lahner, B., Cichy, R.M., and Oliva, A. (2019). Reliability and Generalizability of Similarity-Based Fusion of MEG and fMRI Data in Human Ventral and Dorsal Visual Streams. *Vision (Basel)* **3**, 8.
- Muckli, L., De Martino, F., Vizioli, L., Petro, L.S., Smith, F.W., Ugurbil, K., Goebel, R., and Yacoub, E. (2015). Contextual Feedback to Superficial Layers of V1. *Curr. Biol.* **25**, 2690–2695.
- Muukkonen, I., Ölander, K., Numminen, J., and Salmela, V.R. (2020). Spatio-temporal dynamics of face perception. *Neuroimage* **209**, 116531.
- Nichols, T., Brett, M., Andersson, J., Wager, T., and Poline, J.-B. (2005). Valid conjunction inference with the minimum statistic. *Neuroimage* **25**, 653–660.
- Pantazis, D., Fang, M., Qin, S., Mohsenzadeh, Y., Li, Q., and Cichy, R.M. (2018). Decoding the orientation of contrast edges from MEG evoked and induced responses. *Neuroimage* **180** (Pt A), 267–279.
- Panzeri, S., Macke, J.H., Gross, J., and Kayser, C. (2015). Neural population coding: combining insights from microscopic and mass signals. *Trends Cogn. Sci.* **19**, 162–172.
- Poser, B.A., and Setsompop, K. (2018). Pulse sequences and parallel imaging for high spatiotemporal resolution MRI at ultra-high field. *Neuroimage* **168**, 101–118.
- Reddy, L., Cichy, R., and VanRullen, R. (2017). Oscillatory signatures of object recognition across cortical space and time. *J. Vis.* **17**, 1346.
- Rosa, M.J., Daunizeau, J., and Friston, K.J. (2010). EEG-fMRI integration: a critical review of biophysical modeling and data analysis approaches. *J. Integr. Neurosci.* **9**, 453–476.
- Salmela, V., Salo, E., Salmi, J., and Alho, K. (2018). Spatiotemporal Dynamics of Attention Networks Revealed by Representational Similarity Analysis of EEG and fMRI. *Cereb. Cortex* **28**, 549–560.
- Seibold, D.R., and McPhee, R.D. (1979). Commonality Analysis: A method for decomposition explained variance in multiple regression. *Hum. Commun. Res.* **5**, 355–365.
- Siegel, M., Buschman, T.J., and Miller, E.K. (2015). Cortical information flow during flexible sensorimotor decisions. *Science* **348**, 1352–1355.
- Stanley, G.B. (2013). Reading and writing the neural code. *Nat. Neurosci.* **16**, 259–263.
- van Kerkoerle, T., Self, M.W., Dagnino, B., Gariel-Mathis, M.-A., Poort, J., van der Togt, C., and Roelfsema, P.R. (2014). Alpha and gamma oscillations characterize feedback and feedforward processing in monkey visual cortex. *Proc. Natl. Acad. Sci. USA* **111**, 14332–14341.
- Vaziri-Pashkam, M., and Xu, Y. (2017). Goal-Directed Visual Processing Differentially Impacts Human Ventral and Dorsal Visual Representations. *J. Neurosci.* **37**, 8767–8782.
- Walsh, V., and Cowey, A. (2000). Transcranial magnetic stimulation and cognitive neuroscience. *Nat. Rev. Neurosci.* **1**, 73–79.
- Walther, A., Nili, H., Ejaz, N., Alink, A., Kriegeskorte, N., and Diedrichsen, J. (2016). Reliability of dissimilarity measures for multi-voxel pattern analysis. *Neuroimage* **137**, 188–200.