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Review article

# Higher and deeper: Bringing layer fMRI to association cortex

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ABSTRACT

Recent advances in fMRI have enabled non-invasive measurements of brain function in awake, behaving humans at unprecedented spatial resolutions, allowing us to separate activity in distinct cortical layers. While most layer fMRI studies to date have focused on primary cortices, we argue that the next big steps forward in our understanding of cognition will come from expanding this technology into higher-order association cortex, to characterize depth-dependent activity during increasingly sophisticated mental processes. We outline phenomena and theories ripe for investigation with layer fMRI, including perception and imagery, selective attention, and predictive coding. We discuss practical and theoretical challenges to cognitive applications of layer fMRI, including localizing regions of interest in the face of substantial anatomical heterogeneity across individuals, designing appropriate task paradigms within the confines of acquisition parameters, and generating hypotheses for higher-order brain regions where the laminar circuitry is less well understood. We consider how applying layer fMRI in association cortex may help inform computational models of brain function as well as shed light on consciousness and mental illness, and issue a call to arms to our fellow methodologists and neuroscientists to bring layer fMRI to this next frontier.

A major outstanding challenge in neuroscience is to integrate across levels of investigation, linking genes, molecules, cells, microcircuits, regions, systems and behavior. This will require bringing together evidence from sources across different spatial scales—from the microscopic, such as electrophysiological recordings in animals, to the macroscopic, such as conventional neuroimaging in humans. The mesoscale technique of depth-dependent fMRI, or "layer fMRI"[1], which can be applied non-invasively in awake, behaving humans, is a critical missing link to bridge this gap. In this perspective, we argue that layer fMRI, having established that it can reliably detect expected patterns of activity in primary cortex, is now ready to tackle mechanisms of higher-order cognition in association regions.

Cortical gray matter is organized into layers with distinct cytoarchitecture, connectivity, and function. In the canonical model of hierarchical connectivity, feedforward connections (i.e., those from lower to higher regions) terminate predominantly in the granular layer (layer IV), while feedback connections (from higher to lower regions) terminate predominantly in infragranular (V and VI) and supragranular (I-III) layers (Felleman and Van Essen, 1991; Maunsell and van Essen, 1983; Rockland and Pandya, 1979). While this influential model appears to broadly describe the organization of mammalian visual systems (where it was initially characterized), more recent evidence suggests that patterns of laminar connectivity may deviate from this canonical model in other systems and/or further up the cognitive hierarchy—i.e., in regions of association cortex (Barbas, 2015; Godlove et al., 2014; Markov et al., 2014; Rockland, 2019). There may also be subtle but important differences in the organization of these circuits between humans and even our closest evolutionary neighbors, making it yet more imperative to complement animal work with human studies.

To date, nearly all layer fMRI studies have focused on unimodal cortex: visual (Kok et al., 2016; Muckli et al., 2015; Scheeringa et al., 2016), auditory (De Martino et al., 2015; Moerel et al., 2019), motor

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[1] Note that we use "layer fMRI" throughout this article to mean spatial resolutions capable of resolving depth-dependent activity, but not necessarily individual cortical layers as defined cytoarchitectonically. The current state of the art typically allows for separating signals into two or three compartments, consisting of "superficial" (approximately corresponding to supragranular layers I-III) and "deeper" (infragranular layers V-VI) layers, or "superficial", "middle" (granular layer IV), and "deeper". Advances in acquisition and analysis strategies may allow future studies to resolve individual cortical laminae.

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(Huber et al., 2017; Persichetti et al., 2020), and somatosensory (Yu et al., 2019)—though see Koster et al. (2018); Finn et al. (2019), and Sharoh et al. (2019) for exciting work in the hippocampus, dorsolateral prefrontal cortex, and the occipito-temporal sulcus, respectively. Many use task paradigms that are expected to modulate the balance of feedforward and feedback influences to primary cortex. Feedforward activity is assumed to preferentially target middle layers, while feedback is assumed to preferentially target either superficial or deeper layers or both, depending on the particulars of the paradigm and the areas involved. These studies have been a fruitful proving ground for layer fMRI: when the signals we observe follow the expected patterns, it helps convince us that they are robust and neural in origin. However, ultimately, studying information transfer along the cortical hierarchy by observing only primary cortex is akin to trying to infer the content of a phone conversation by listening to only one side. We argue that layer fMRI is now at a point where it is possible—and indeed, desirable—to move beyond primary cortex into higher-order regions of association cortex.[2]

## 1. Potential applications of layer fMRI in higher-order brain regions

What types of cognitive phenomena might we investigate with layer fMRI? Below, we outline three domains where applying layer fMRI to association cortex could yield new insights into high-order cognition.

### 1.1. Perception and imagery

Memory and imagery share many of the same brain regions and general mechanisms as perception: for example, in the visual system, simply remembering or imagining something activates areas of visual cortex in a grossly similar way as actually perceiving something via retinal input (Dijkstra et al., 2019; Kosslyn et al., 2001). Yet activity patterns associated with perception and imagery are not identical (Lee et al., 2012), and longstanding neuropsychological evidence from patients with cortical damage suggests the two are dissociable (Butter et al., 1997; Sirigu and Duhamel, 2001). More recent work suggests that there are subtle differences between laminar patterns of activity in perception versus imagery in primary cortex (van Kerkoerle et al., 2017). At the same time, there is clear evidence that association cortex—particularly prefrontal and parietal areas—has a role in generating and maintaining imagined representations (Nobre et al., 2004), particularly as they relate to task demands (Bugatus et al., 2017; Lee et al., 2013). A complete understanding of perception and imagery, and what distinguishes them, will require measuring simultaneously from primary cortex and higher-order cortex, as many differences could be encoded not only in laminar activity patterns in primary cortex (Persichetti et al., 2020; Turner, 2016), but also—or uniquely—in laminar activity patterns in higher-order regions, and/or layer-specific interactions between primary and higher-order regions. Simultaneous measurements from both primary and higher-order regions would help validate and extend longstanding claims about the roles of bottom-up versus top-down processes in perception and imagery, respectively (Dentico et al., 2014; Dijkstra et al., 2019; Mechelli et al., 2004).

### 1.2. Attention

Another phenomenon that could benefit from study with layer-specific tools is attention. Attention is one of the most powerful ways we can modulate our own sensory responses to the external world. Many studies have capitalized on this by manipulating selective attention and observing effects on spatiotemporal patterns of cortical activity to otherwise identical stimuli (De Martino et al., 2015; Gau et al., 2020; Guo et al., 2020; Klein et al., 2018). Yet to date nearly all layer-specific studies of attention have recorded exclusively in primary or unimodal cortex, whereas top-down attentional control is thought to originate from high-order areas in prefrontal and parietal cortex (Squire et al., 2013). Understanding how attention is implemented in the dynamics of top-down and bottom-up pathways, as well as refining and expanding upon computational models of attention (Corchs and Deco, 2002), will require empirical measurements from both higher and lower areas.

### 1.3. Predictive coding

Yet a third concept, related in broad strokes to the phenomena discussed above, is predictive coding and other hierarchical theories of brain function (Friston, 2005; Rao and Ballard, 1999). These theories hold that the brain is fundamentally a prediction engine: higher areas generate predictions and relay them to lower areas via feedback connections, while lower areas receive sensory inputs and send them, along with prediction errors, up the hierarchy via feedforward connections. Feedforward and feedback paths are distinguished by cortical depth: feedforward connections originate from superficial layers and terminate in middle layers, while feedback connections predominantly arise from lower layers and terminate in both superficial and deep layers, avoiding middle layers (Bastos et al., 2012). While these theories are compelling and influential, many of their tenets—including the assumed laminar circuitry—still await direct empirical verification (Stephan et al., 2017).

Layer fMRI studies have begun to develop paradigms and test hypotheses consistent with the predictive coding framework (Kok et al., 2016; Muckli et al., 2015). But to date, nearly all work has been focused on primary cortex, leaving authors to merely speculate as to the source region(s) giving rise to the predictions, and the intrinsic dynamics of these prediction-generating regions. Now is an opportune time for studies situated within the framework of predictive coding to leverage fMRI's main advantage—its wide-field capacity—to extend their measurements to association regions, and thereby achieve a more complete picture of predictive circuits.

## 2. Methodological considerations for layer fMRI in higher-order regions

Layer fMRI in association cortex is quite achievable, though not without difficulties. Below, we show preliminary data demonstrating this feasibility, as well as briefly review challenges and potential solutions. These include practical challenges to acquiring and analyzing data, as well as theoretical challenges to generating hypotheses, choosing experimental paradigms, and interpreting results.

Note that there are several outstanding issues and limitations to layer fMRI in general, including issues with distortion, smoothing, and achieving spatial specificity in the face of venous artifacts at the cortical surface. These challenges, and methods to overcome them, are reviewed extensively elsewhere (Kashyap et al., 2018; Polimeni et al., 2018), including other articles in this issue. Here, we focus on additional considerations that arise when applying layer fMRI in association cortex.

### 2.1. Feasibility of layer fMRI in association cortex

We include here some preliminary data showing feasibility of measuring depth-dependent signal in higher-order brain regions. Fig. 1 shows data from a recent resting-state experiment acquired at 7 T using

[2] It is our view that a complete understanding of the role of laminar circuitry in supporting cognition will ultimately require a whole-brain systems perspective, integrating across primary, association, subcortical, and cerebellar regions. In an attempt to keep this article clear and focused, we chose to concentrate on association cortex in particular, since these regions carry some unique challenges and opportunities for experimental design, acquisition and analysis.

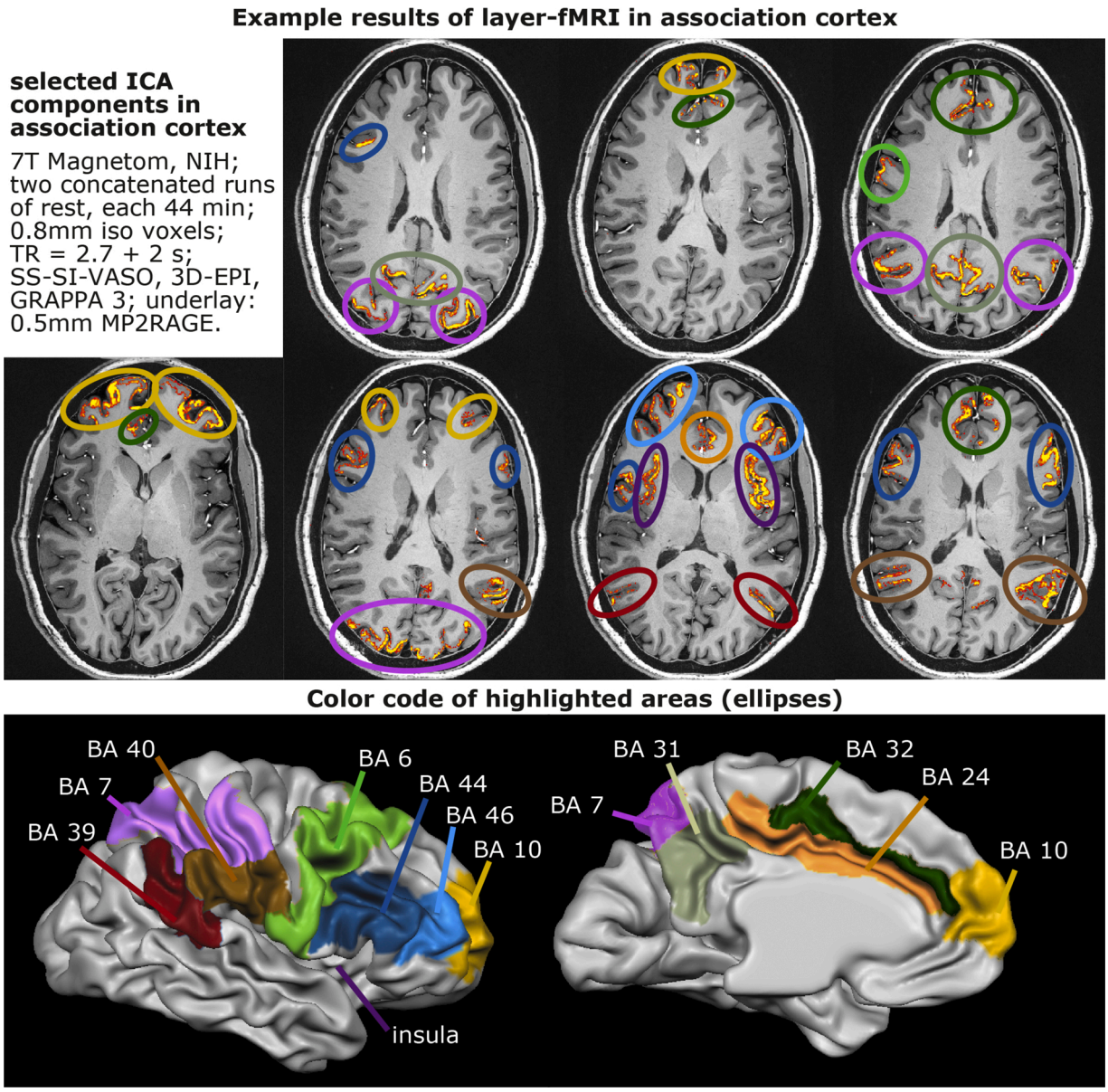


**Fig. 1. Feasibility of layer fMRI in association regions.** The purpose of this figure is to show that state-of-the-art layer-fMRI sequences are capable of capturing sub-millimeter (voxel size 0.8 mm isotropic) brain activity across many higher-order brain areas. Data shown here are from a single representative participant of a larger study described in Huber et al. (this issue). Data were acquired on the 7 T Magnetom in the Section on Functional Imaging Methods at the National Institute of Mental Health, with an SS-SI-VASO sequence (slice-saturation, slab-inversion, vascular space occupancy) during an 89 min functional resting-state experiment.

a state-of-the-art functional sequence with 0.8 mm isotropic voxels. The data-driven approach of independent components analysis (ICA) helps avoid the need for *a priori* ROIs, which can be more challenging to define in non-primary regions (discussed further in the following two sections). ICA yields signals that appear clean and reasonable (Fig. 1)—i.e., they are localized to gray matter, and are consistent with known functional networks involving higher-order regions (e.g., default mode, fronto-parietal, salience). This helps give us confidence that layer-dependent signals can be recovered both outside of primary cortex and in the absence of strong task-evoked modulation. Fig. 2 explores these same data in further detail to show that different regions of association cortex have different layer profiles—in other words, overall signal of a region may be dominated by superficial, middle, or deeper layers, or some combination.

Fig. 2 also highlights the need for region-specific normalization of MRI-based "layers" with ground-truth cytoarchitecture, since, just as in primary cortex, the position and relative thickness of different layers can vary substantially across regions of association cortex. In light of this variation, accurately visualizing and interpreting depth-dependent fMRI signals relies heavily on evidence from histology as well as *in vivo* and *ex vivo* anatomical imaging techniques such as diffusion MRI (Roebroeck et al., 2019), T1-weighted imaging for myeloarchitecture (Dinse et al., 2015), and magnetic susceptibility imaging (Deistung et al., 2013). Ongoing efforts to create whole-brain laminar atlases with increasing detail and resolution (Trampel et al., 2019; Wagstyl et al., 2020) will greatly benefit depth-dependent functional imaging in association cortex as well as across the whole brain.

### 2.2. Practical challenges: acquisition

Association cortex, especially the parietal and prefrontal lobes, is highly variable across individuals in both its structure and functional anatomy (Mueller et al., 2013). Unlike primary regions that often have identifiable landmarks, such as the Stria of Gennari in the primary visual

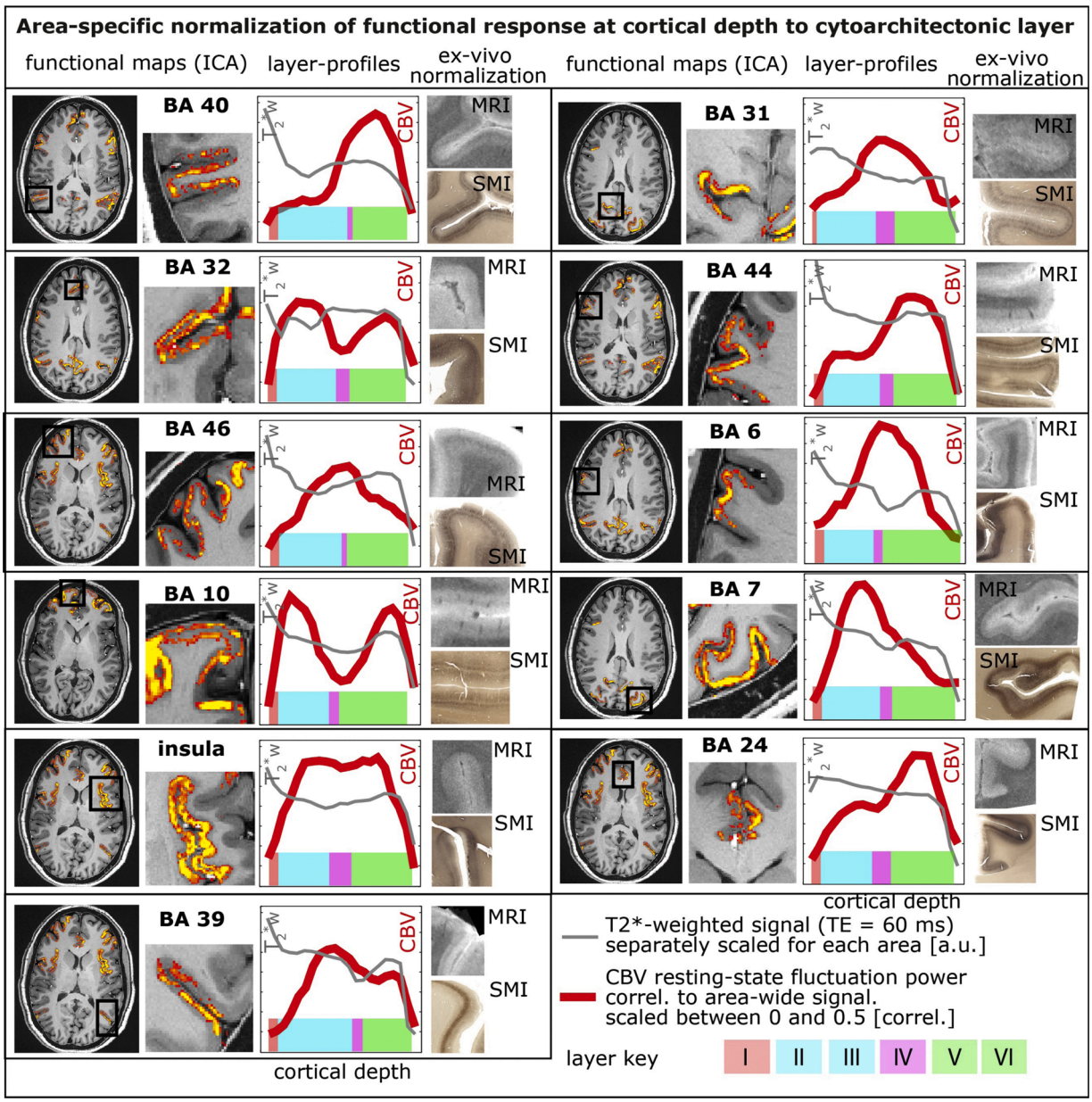


**Fig. 2. Exploring layer profiles for various regions of association cortex.** This figure demonstrates the variability of layer-fMRI results across the wide spectrum of higher-order brain areas. The left two columns ("functional maps") highlight various layer-specific activity features across brain areas; some areas show largest signal activities in the superficial layers (e.g., Brodmann area [BA] 7), some areas show largest signals in the deeper layers (e.g., BA 40), some areas show both (e.g., BA 10), and some areas have rather unspecific responses (e.g., insula). The corresponding red layer-profiles (middle graphs) refer to the overall layer-dependent fluctuation power of this brain area (note, this does not require the manual selection of components from an independent components analysis [ICA]). These data refer to the same study that is mentioned in Fig. 1. The right column ("ex-vivo normalization") depicts how the structural layer location is also highly variable across association areas. The thicknesses and the location of each cytoarchitectonically defined cortical layer are slightly different. Thus, for proper interpretation of the depth-dependent functional results, ex-vivo atlases and depth-normalizations are vital. Here, the thickness and location of each cytoarchitectonical cortical layer is normalized based on the FLASH (TE = 60 ms) and histology (SMI-32) atlas from Ding et al. (2016).

cortex or 'hand knob' in the primary motor cortex, functional subdivisions of association cortex are difficult to pinpoint in individual subjects by macroscale anatomical features alone. This can pose challenges for both acquisition and analysis.

Because most of the early layer fMRI sequences could not offer whole-brain coverage at the resolutions necessary to resolve depth-dependent activity, experimenters were limited to a partial field of view, which had to be placed over the desired brain area in real time (i.e., while the participant was in the scanner, before the start of the high-resolution experiments). A misplaced slice prescription could mean failure to optimize signal acquisition in the most important region(s), or missing the area of activation entirely. Yet, especially in association cortex, the lack of anatomical landmarks makes it difficult to place slices based on a structural localizer alone. One solution is to conduct an online functional localizer at standard resolution at the beginning of the scan session, using a similar or identical task paradigm as the one used for high-resolution scans. If the task modulation is sufficiently strong—and it is advisable to use strong tasks for layer fMRI—the real-time general linear model capabilities should reveal the "hotspot" that can be used for subsequent slab positioning.

Acquisition methods for layer fMRI are improving rapidly, and whole-brain (or near whole-brain) coverage is now possible with certain

pulse sequences. Whole-brain acquisitions largely obviate the need for online functional localizers (though if there are substantial signal inhomogeneities across the field of view, experimenters might still find them useful to help optimize signal quality in the main region(s) of interest). But these whole-brain sequences often have caveats: the wide-field spatial resolution may come at the cost of temporal resolution (in the case of cerebral blood volume (CBV)-based sequences e.g., vascular space occupancy (VASO), which requires an inversion pulse and acquisitions interleaved with BOLD), or depth specificity (in the case of GE-BOLD, which is prone to draining vein artifacts at the cortical surface). Long TRs may be acceptable for certain paradigms, but others may require a faster sampling rate, especially the event-related designs that are often best suited for probing nuanced cognitive processes (discussed further below). Our current recommendation is that experimenters consider tradeoffs between spatial resolution, spatial specificity, imaging field of view, and temporal resolution in selecting the most appropriate acquisition method for their particular study, noting that these tradeoffs may be different for studies of higher-order versus primary cortex.

### 2.3. Practical challenges: analysis

An ongoing challenge to analyzing layer fMRI data from association cortex is how to resolve depth-dependent signals with respect to cortical laminae defined based on cytoarchitecture. While current layer fMRI sequences offer spatial resolutions as high as 0.5 mm, this is not enough to resolve structural landmarks of all six individual cytoarchitectonically defined layers with Nyquist sampling in the functional data. In primary cortex, which has been heavily investigated in the last century, a clear correspondence between relative cortical depths and respective partial voluming of canonical laminae has been established, making it relatively straightforward to interpret functional signal in primary areas with respect to true underlying cortical layers. However, in association regions, the relationship between relative depth and underlying layers is highly variable (Wagstyl et al., 2020) and less well investigated. Thus, interpretating layer fMRI results is more difficult in association cortices compared to primary cortices. Future layer fMRI studies in association cortex will need to build additional groundwork to relate cortical depths to cytoarchitectonic cortical layers. Analogous to our previous study (Finn et al., 2019), this can be achieved using ex-vivo atlases that have both histology and MRI components (Amunts et al., 2013; Ding et al., 2016). In any case, the increased complexity of the correspondence between cortical depths and cell-type-specific layer communications further underscores the importance of applying layer fMRI in association areas.

Another challenge to layer fMRI in association cortex concerns how best to model and interpret task-evoked signal changes. Traditional fMRI activation analyses rely heavily on the general linear model (GLM), in which a model of the task is convolved with an assumed hemodynamic response function and compared to observed brain signal timecourses. However, results of depth-dependent GLMs can be hard to interpret for the following reasons: (1) signal amplitude, quality and stability are heterogeneous across cortical depths; (2) the hemodynamic response function varies across cortical depths (Uludağ and Blinder, 2018); and (3) the baseline blood volume distribution varies across the cortical depth. Most layer fMRI studies in primary cortex use block designs (Gau et al., 2020; Huber et al., 2017), which are relatively less dependent on the particulars of deconvolution and thus enjoy higher detection power—an important advantage in the signal-starved world of high-resolution fMRI. But to probe increasingly nuanced aspects of cognition in high-order regions, the flexibility of event-related designs can help disentangle neural activity to distinct subprocesses of a complex cognitive function. Event-related designs can also minimize participant habituation and anticipation, which may be more problematic as one moves up the cortical hierarchy. In our recent study (Finn et al., 2019), we used an event-related design where trials were sufficiently long to permit averaging of raw trial timecourses, without the need to deconvolve the hemodynamic response. Then, we could directly compare magnitude and depth-dependent location of evoked activity during different periods within the trial. While more rapid event-related designs may still be tricky, we expect that ongoing efforts to improve temporal resolution during acquisition, as well as refine hemodynamic models for analysis (Havlicek and Uludağ, 2020), will allow us to use deconvolution-based analyses with more confidence. Other ways to mitigate biases of layer-dependent differences in the hemodynamic response function include conducting the GLM analysis based on impulse response functions, or estimating (i.e., calibrating) the layer-dependent HRF from an independent dataset (Fracasso et al., 2016; Silva et al., 2007). These approaches, however, can come along with more degrees of freedom or longer scan durations.

Finally, the need to preserve as much spatial precision as possible in layer fMRI studies make it difficult to perform the nonlinear registration step (e.g., to a template brain) typical of standard-resolution fMRI studies. This is a challenge for all layer fMRI work, but may be even more problematic for studies of association cortex, since these areas are typically more variable in their anatomy across individuals, as discussed above. In many cases, the need for nonlinear registration can be obviated altogether by simply performing analyses in single-subject space. Numerical signals can then be statistically combined at the final step for group-level inferences. If possible, displaying single-subject data in addition to group-level statistics is to be encouraged, to help convey how robust and replicable the phenomena are across subjects (Finn et al., 2019; Sharoh et al., 2019).

### 2.4. Theoretical challenges and paradigm selection

Another set of challenges surrounds generating hypotheses to test with layer fMRI in association cortex. In their excellent article, Lawrence et al. (2019) outline many areas where layer fMRI might be brought to bear on pressing questions in cognitive neuroscience. Yet while they provide compelling examples for how to apply the technique to such phenomena as working memory, selective attention, and multisensory integration, most of the specific hypotheses they offer are framed around expected patterns of activity in primary cortex. For example, they note that effects of selective attention in the relevant sensory cortex would be expected to be most pronounced in superficial and deep layers (consistent with the feedback input pattern), but stop short of hypothesizing what a layer-specific signature of attention might look like in the higher-level regions that are presumably generating the attention in the first place.

In many respects, this is understandable. As mentioned above, it is an open question whether the canonical model of layer-specific inputs and outputs to a cortical column, originally defined in primary cortex, holds true in association cortex, which makes it hard to develop clear hypotheses for these regions. But we caution researchers against avoiding these areas altogether, lest we fall into a chicken-and-egg trap: the only way to increase our understanding of the circuitry is to measure from these regions, attempt to interpret activity patterns in light of existing knowledge, and use empirical data to iteratively refine our theories, hypotheses, and experimental designs. We argue that layer fMRI is now at a point where we can expand from tightly controlled experiments in sensory cortex with clear hypotheses—which were necessary to show feasibility of the technique—to more exploratory, data-driven investigations of functional dynamics both across the cortical hierarchy as well as within higher-order regions themselves.

Open-ended paradigms like resting state and naturalistic tasks are good candidates for such exploratory studies. Resting-state acquisitions can be used to investigate layer-specific functional connectivity both within high-order and between primary and high-order regions (Huber et al., this issue). Data acquired during naturalistic stimulation—e.g., movie watching—lend itself to both connectivity and activation analyses. Notably, an identical “ground truth” stimulus across subjects

permits analyses such as inter-subject correlation (Hasson et al., 2004; Nastase et al., 2019), in which an activity timecourse from one subject's brain is correlated with the timecourse from the same spatial location in a second subject's brain (or with a different spatial location, in the case of inter-subject functional connectivity (ISFC; Simony et al., 2016)). In fMRI studies at standard resolution, rich, engaging stimuli tend to synchronize activity across individuals not only in sensory regions, but also in association regions. Layer fMRI studies with naturalistic paradigms could reveal the extent to which this synchrony is layer-specific, and by extension, layer inter-subject functional connectivity (i.e., cross-subject, cross-region, cross-layer correlations) may reveal directed interactions (see Fig. 3 for a schematic). Unlike within-subject functional connectivity, in which much of the noise is correlated across spatial locations, inter-subject functional connectivity helps isolate signal that is neural in origin. Just as in other layer fMRI studies, it would be important to use robust functional localizers and perform all layer segmentation in individual subject space. Layer-average signals could then be extracted and used as input to the cross-subject analyses, which would obviate the need to register different brains in high-resolution space and minimize concerns about partial volume effects or anatomical variability across subjects. Future studies could also explore the utility of functional alignment approaches such as hyperalignment (Haxby et al., 2011) or shared response modeling (Chen et al., 2015) to achieve an accurate separation of layer sources and ensure correspondence across subjects.

A single time-locked stimulus also enables averaging of timecourses within subjects across repeated viewings, which is not possible with resting-state data and may also improve signal-to-noise ratio for depth-dependent analyses in individuals. This may be of particular value in association regions, where magnitude of evoked activity tends to be small relative to ongoing spontaneous fluctuations.

On a methodological note, invasive recordings in non-human primates can achieve unrivaled precision, but their measurements are typically limited to one or a small number of regions at a time. Layer fMRI is the most promising tool we have for gaining a wide-field view of depth-dependent cortical dynamics in many (or, optimistically, all) brain regions simultaneously. We expect that ongoing dialogue between layer fMRI in humans and electrophysiological studies in animal models, where experiments are increasingly using depth-dependent electrodes capable of separating sources from different layers within a cortical column (Bastos et al., 2018; Markowitz et al., 2015), will benefit the field as a whole as we seek to develop and refine models of cortico-cortical interactions. Specifically, ongoing efforts to benchmark layer fMRI by means of cross-species comparisons with similar tasks (Self et al., 2019) and concurrent layer-fMRI with electrophysiology (Boorman et al., 2010) will provide more confidence in the neuroscientific interpretability of layer fMRI results. For more in-depth discussion of validating layer fMRI and linking electrophysiology and layer fMRI, see other articles of this special issue.

## 3. On the horizon

In this final section, we consider how bringing layer fMRI to association cortex may help improve computational models of the brain, as well as shed light on some of the biggest questions in neuroscience: what gives rise to conscious experience, and how cortical information processing goes awry in mental illness.

### 3.1. Informing macroscale computational brain models

Recent years have seen considerable progress in computational models that simulate macroscale features of brain dynamics using networks of interconnected regions (Deco and Kringelbach, 2014; Gu et al., 2015; Heitmann et al., 2018; Honey et al., 2007; Ritter et al., 2013; Sanz Leon et al., 2013). These "synthetic brains" are built by optimizing their fit to empirical data, which typically include a structural backbone measured with anatomical tract imaging (e.g., diffusion tensor imaging), plus functional data from either electromagnetics (e.g., electroencephalography [EEG]), hemodynamics (e.g., fMRI), or both. While these models are increasingly successful at reproducing observed brain dynamics, they are only as good as the empirical data used to develop and

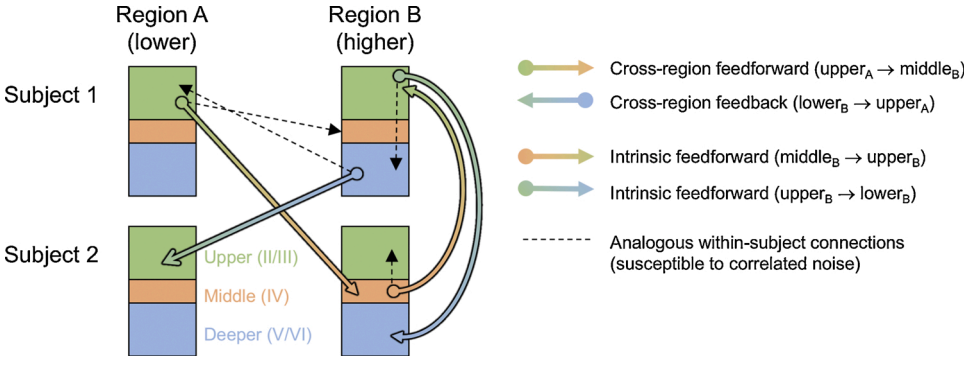


**Fig. 3. Layer-specific inter-subject functional connectivity.** A schematic for how layer-specific ISFC during naturalistic tasks could be used to uncover directed interactions across the cortical hierarchy. Unlike within-subject layer-specific connectivity, cross-subject layer-specific connectivity is expected to be free from correlated noise across layers and regions, meaning it is more likely to be purely neural in origin. Connections of interest are depicted using color-coded arrows, with the hypothesized direction of each connection indicated by the arrowheads. For example, feedforward activity between a lower region (A) and a higher region (B) could be measured by correlating upper layer activity in region A in Subject 1 with middle-layer activity in region B in Subject 2. (Note that the inverse correlations could also be calculated—e.g., from upper$_A$ in Subject 2 to middle$_B$ in Subject 1—but are not shown here for clarity). For each connection, the analogous within-subject connection is indicated with a dotted black line. While depicted connections are inspired by the canonical cortical microcircuit model (Bastos et al., 2012), we note again that this model may not fully generalize to laminar circuitry in higher-order regions; therefore, we also suggest data-driven investigations of layer-specific ISFC to identify different or additional connections that may be present within and between these parts of cortex.

refine them. Many models have a strong temporal component, for which EEG is the preferred input modality due to its vastly superior temporal resolution and tighter relationship to neuronal activity. However, one limitation of EEG is that it mainly reflects activity in excitatory superficial-layer neurons, as these are closest to the skull and oriented perpendicular to the scalp (Buzsáki et al., 2012). Thus, it may give an incomplete picture of cortical dynamics by missing activity in middle and deeper layers; incorporating data from layer fMRI can help fill this gap. A second limitation is that directionality of connections is often inferred from time- or phase-lags between regions, which are much more trustworthy in EEG than in hemodynamic signals (where the slow and spatially variable hemodynamic response function muddies their interpretation), but are nonetheless an indirect measure of causality. Layer fMRI, while also indirect, can provide a complementary source of evidence to help infer directionality based on known laminar-specific patterns of feedforward and feedback activity. In all cases, because intrinsic and cross-regional dynamics can be substantially different between sensory and association regions, it will be critical to incorporate empirical layer fMRI data from both primary and higher-order regions to faithfully synthesize dynamics across the cortical hierarchy.

### 3.2. Consciousness

Influential theories of consciousness posit that awareness arises from the interplay between lower and higher areas; neither is sufficient on its own (Tong, 2003). When consciousness is disrupted—for example, via anesthesia—cortex shows altered activity dynamics both within and across primary and higher-order regions. For example, in animal models, anesthesia substantially alters activity to visual stimulation not only in V1, where it strengthens evoked responses (a quantitative change), but also in PFC, where it dramatically disrupts the pattern of responses (a qualitative change) (Sellers et al., 2013). The functional connectivity (i.e., cross-regional coherence) between the two is also affected, and in both regions, the observed changes are to some extent layer specific (Sellers et al., 2015). In other words, anesthesia does not simply "knock out" prefrontal cortex while leaving unimodal cortex unchanged; rather, it affects both types of regions in terms of both their intrinsic dynamics as well as how they respond to perceptual input. Similarly, lesion studies in humans suggest that both primary and higher-order regions play distinct roles in generating conscious experience (Aru et al., 2012; Koch et al., 2016; Lau and Rosenthal, 2011).

If bottom-up sensory signals to primary cortex alone are not enough to evoke consciousness, but rather, awareness stems from top-down recurrent processing of these signals by higher-order regions (Crick and Koch, 2003; Lamme, 2000; Meyer, 2011; Pollen, 1995, 1999), then the resulting signatures of consciousness are expected to show laminar specificity, in accordance with what we know of cortico-cortical circuitry. Layer fMRI, then, will be an essential tool to advance the study of consciousness (Schneider et al., 2019)—but only if we turn our focus to include association cortex as well as primary regions.

### 3.3. Pathology

Many of our most sophisticated cognitive functions—memory, attention, language—are disrupted in mental illness. To the extent that layer fMRI can reveal the circuitry that instantiates these functions, it could also reveal how this circuitry is disrupted in patients suffering from psychiatric conditions (Stephan et al., 2017). These illnesses are complex, and multiple disruptions, either from a common source or distinct sources, may afflict multiple regions along the cortical hierarchy. However, there is longstanding evidence that certain illnesses preferentially affect association cortex. Schizophrenia, for example, is associated with pathology in the dorsolateral prefrontal cortex; intriguingly, this pathology often shows a laminar-specific signature. In particular, postmortem studies report that the density and morphology of excitatory pyramidal cells is reduced in layer III (Glantz and Lewis, 2000; Rajkowska et al., 1998), while astroglia are reduced in layer V (Rajkowska et al., 2002). Previous fMRI studies at standard resolution showed altered overall activity levels in dlPFC in patients with schizophrenia (Weinberger et al., 1986), especially during demanding cognitive tasks such as working memory (Cameron S. Carter et al., 1998; Perlstein et al., 2001), but were not able to localize disruptions to specific cortical layers. In our recent study, we localized component subprocesses of a working memory task—i.e., delay, response—to different layers within dlPFC in healthy volunteers. An exciting next step would be to conduct this layer fMRI experiment in patients with schizophrenia, to determine if this layer-specific hypofunctionality can be observed in real time.

Another way in which layer fMRI might advance our understanding of mental illness is by providing clues as to which cortical cell population(s) are dysfunctional. Although isolating activity in specific cell types and/or neurotransmitter systems is typically not possible using traditional endogenous fMRI contrast mechanisms, with layer fMRI we may be able to infer the source of activity at a more mechanistic level than previously possible—e.g., by capitalizing on the fact that cell and receptor types are distributed differently across layers. In combination with work in animal models, this may help to identify and test novel targets for pharmacological intervention. This could also help inform computational brain models discussed above.

Finally, populations with developmental deviations from typical cortical formation, such as those with congenital microcephaly, could provide another valuable window into how layer-specific neural organization supports cognition and behavior. Even mild microcephaly is associated with a reduction in gray matter of up to 40 percent (Sylvester, 1959), and superficial layers may be disproportionately affected (Hammarberg, 1895; Yu et al., 2010). Studying these individuals using layer fMRI techniques could give insight into the degree to which laminar function and circuits are plastic, and, combined with a characterization of cognitive phenotypes, the degree to which their typical organization constrains "normal" brain function.

### 3.4. Conclusion

We believe that layer fMRI, having proven itself robust and reliable in the testing grounds of primary cortex, is now at a point where it can and should be brought to bear on some of the biggest questions in cognitive neuroscience. We hope this call to arms inspires other researchers to expand their fields of view, literally and figuratively, into the most highly evolved regions of the brain, to study the underpinnings of our most canonically human capacities.

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## Appendix A. The Peer Review Overview and Supplementary data

The Peer Review Overview and Supplementary data associated with this article can be found in the online version: https://doi.org/10.1016/j.pneurobio.2020.101930.

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