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Ultra-High Field Imaging of Human Visual Cognition

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Abstract

Functional magnetic resonance imaging (fMRI), the key methodology for mapping the functions of the human brain in a noninvasive manner, is limited by low temporal and spatial resolution. Recent advances in ultra-high field (UHF) fMRI provide a mesoscopic (i.e., submillimeter resolution) tool that allows us to probe laminar and columnar circuits, distinguish bottom-up versus top-down pathways, and map small subcortical areas. We review recent work demonstrating that UHF fMRI provides a robust methodology for imaging the brain across cortical depths and columns that provides insights into the brain's organization and functions at unprecedented spatial resolution, advancing our understanding of the fine-scale computations and interareal communication that support visual cognition.

INTRODUCTION

In the past four decades, functional magnetic resonance imaging (fMRI) has become the key methodology for researchers and clinicians to visualize neural activity in the human brain in a noninvasive manner (Bandettini et al. 1992, Kwong et al. 1992, Ogawa et al. 1992). Many fMRI studies provide insights into the brain's organization and functions. For example, researchers have identified key regions involved in perceptual (e.g., the fusiform face area, specialized for face perception) and cognitive (e.g., frontoparietal regions involved in working memory) processes (Ester et al. 2015, Jia et al. 2021a, Kanwisher et al. 1997) and revealed distinct brain networks (e.g., the ventral and dorsal attentional network, default mode network) that are shown to support complex cognitive functions in health and disease (van den Heuvel & Sporns 2019, Yu et al. 2021). Despite the widespread adoption of 3 Tesla (3T) fMRI, several limitations remain, challenging the interpretation of fMRI signals. First, the blood-oxygen-level-dependent (BOLD) signal reflects changes in blood oxygenation and is an indirect measure of the neural activity. Second, inferring directionality in information flow or drawing causal inferences is limited by the low temporal resolution of fMRI (in the order of seconds). Third, the BOLD signal is contaminated by vasculature-related and partial volume effects that reduce spatial resolution, making it difficult to distinguish underlying computational processes.

Recent advances in ultra-high field (UHF) imaging techniques provide a mesoscopic tool (**Figure 1**) that enables us to interrogate brain computations at a finer scale (i.e., submillimeter resolution) than that afforded by standard 3T fMRI (Goense et al. 2016). In particular, UHF fMRI allows us to probe cortical layers that are known to have distinct connectivity with upstream and downstream areas, allowing us to discern bottom-up versus top-down pathways and infer the direction of information flow across areas. Furthermore, UHF fMRI enables us to map small subcortical areas [e.g., the lateral geniculate nucleus (LGN), habenula] and columnar organization

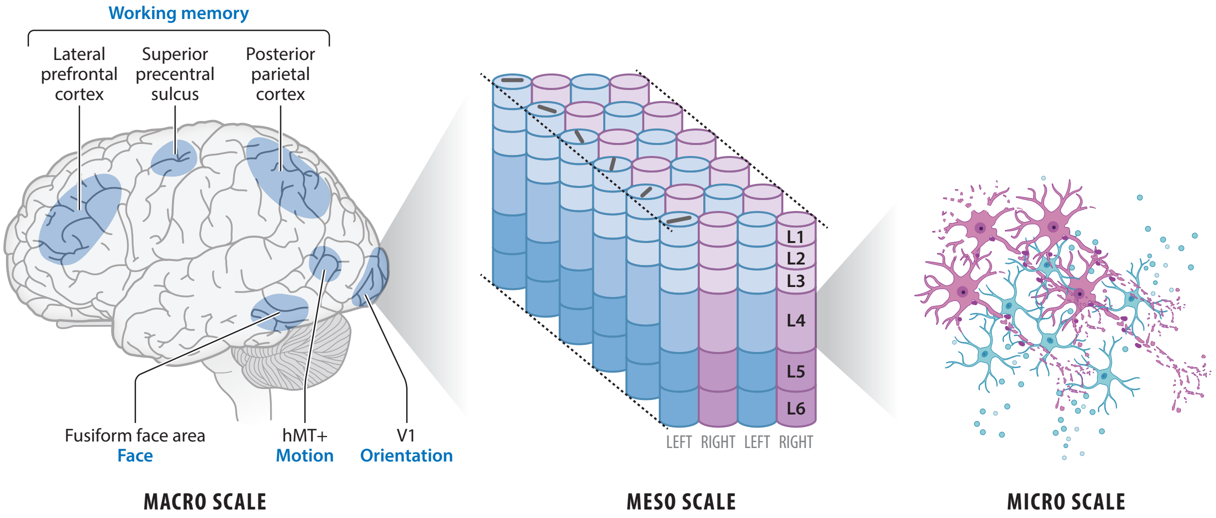

Figure 1

Ultra-high field functional magnetic resonance imaging provides a mesoscopic tool that allows us to probe laminar and columnar circuits, bridging the gap between microscale neurophysiology and macroscale neuroimaging studies. Abbreviation: hMT+, human middle temporal area.

[e.g., ocular dominance columns (ODCs), orientation columns], allowing us to characterize fine-scale activity that supports intra-areal computations.

We review recent advances in UHF fMRI in visual and cognitive neuroscience, complementing previous work reviewing data acquisition methods (Jia et al. 2021b, Kashyap et al. 2018, Koopmans & Yacoub 2019), analysis approaches (Kemper et al. 2018, Polimeni et al. 2018), and clinical applications (Barisano et al. 2019, Rutland et al. 2020, Trattnig et al. 2018). We focus on recent work showing how UHF fMRI across cortical depth advances our understanding of the brain circuits supporting a range of perceptual and cognitive functions, including 3D perception (Ng et al. 2021), motion perception (Schneider et al. 2019), adaptive sensory processing (Zamboni et al. 2020), perceptual learning (Jia et al. 2020), visual attention (Gau et al. 2020, Lawrence et al. 2019, Liu et al. 2021), and working memory (Finn et al. 2019, Lawrence et al. 2018). Furthermore, we discuss how UHF fMRI can be used to map cortical columnar organization and subcortical areas (Cheng 2018, Qian et al. 2020) and review key challenges related to methodological limitations and future potential developments to bridge the gaps among brain mapping studies across scales.

USING ULTRA-HIGH FIELD FUNCTIONAL MAGNETIC RESONANCE IMAGING ACROSS CORTICAL DEPTH TO INTERROGATE INFORMATION PATHWAYS

The visual cortex of the primate brain is stratified into six distinct layers linking to different brain computations (feedforward versus feedback). In particular, sensory inputs enter the primary visual cortex (V1) from the thalamus at the level of the middle layer (layer 4), and the output is fed forward from the superficial layers (layer 2/3), while feedback information is exchanged primarily between deeper (layer 5/6) and superficial layers (Larkum et al. 2018, Markov et al. 2014, Rockland & Pandya 1979, Self et al. 2019). Horizontal connections across V1 columns predominantly terminate in superficial layers (Douglas & Martin 2007, Gilbert & Wiesel 1983) and are suggested to support recurrent processing within the visual cortex (Schwabe & Obermayer 2005, Self et al. 2013). The human neocortex in the calcarine sulcus, the location of V1 in the human brain, is only approximately 1.8 mm thick (Salat et al. 2004). As the acquisitions of neural signals from small voxels suffer from low signal-to-noise ratio (SNR) and small brain coverage, our ability to measure brain activity from each single layer with fMRI remains limited. However, using UHF fMRI at 7 Tesla (spatial resolution of 0.6–0.8 mm isotropic), it is currently feasible to discern brain signals across cortical depth in three (superficial, middle, and deeper) functional layer compartments that coarsely correspond to different pathways (i.e., feedforward, feedback, and recurrent processing) (**Figure 2**).

Recent work combining UHF fMRI with elegant experimental designs and computational analysis approaches provides evidence that UHF fMRI can be used reliably to discern layer-specific processing and information pathways. Evidence for this comes, for example, from studies investigating contextual influences in visual processing. In particular, eliminating feedforward signals in subregions of the visual cortex by occluding image parts resulted in decodable information appearing in a superficial layer region in the visual cortex corresponding to the occluded location (Muckli et al. 2015). Similarly, a study using illusory contours (i.e., a Kanizsa triangle comprising three disks) showed that the illusory contours predominantly activated V1 deeper layers (Kok et al. 2016), while the inducing disks (i.e., after rotating to disrupt the perception of an illusory triangle) activated all cortical layers. These layer-specific responses in superficial and deeper layers have been suggested to reflect feedback rather than feedforward processing. Complementary to this work on sensory processing, similar layer-specific activations have been

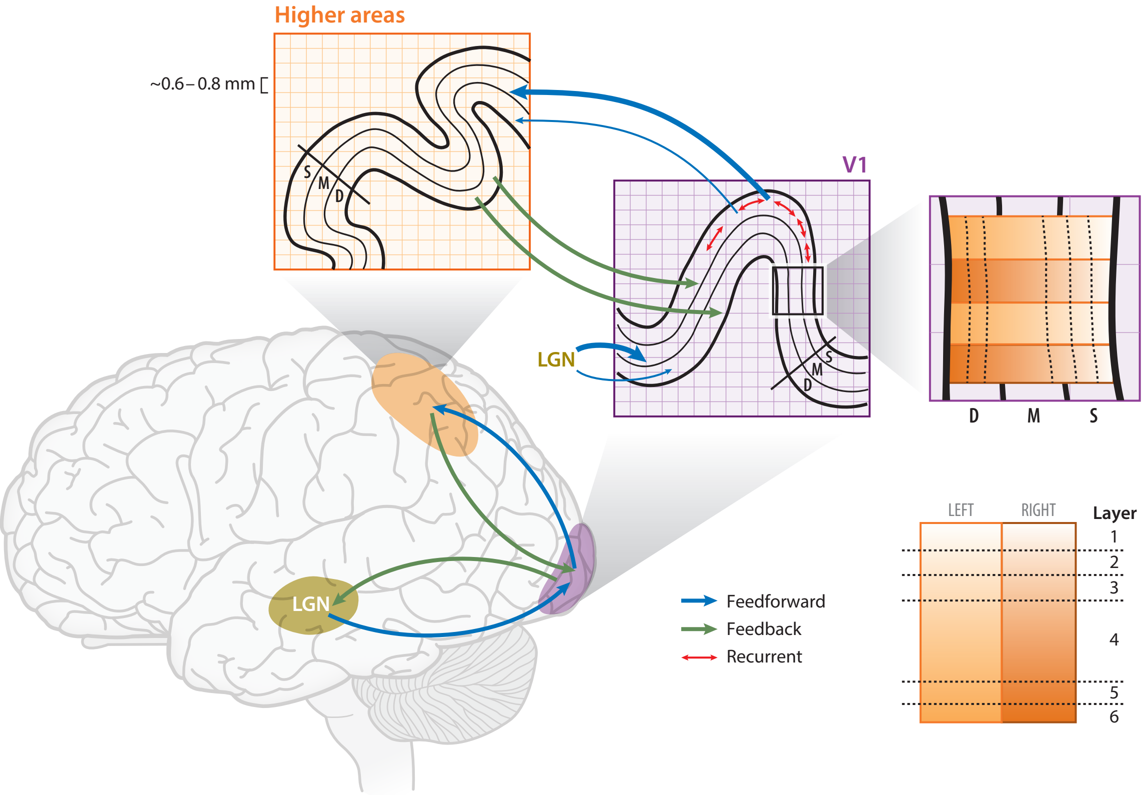

Figure 2

Schematic representation of the information flow across brain areas and cortical depth based on known anatomical circuits. Feedforward processing mainly engages middle (M) and deeper (D) layers of downstream brain areas (*blue arrows*), whereas feedback information is exchanged primarily between deeper and superficial (S) layers (*green arrows*). Horizontal connections across V1 columns (e.g., left eye versus right eye) predominantly terminate in superficial layers (*red arrows*). Abbreviation: LGN, lateral geniculate nucleus.

observed for higher cognitive processes that are known to influence sensory processing. For example, prior expectations were shown to selectively affect activity in V1 deeper layers, consistent with feedback processing in the context of predictive coding (Aitken et al. 2020).

Taken together, although UHF imaging resolution does not support one-to-one mapping between magnetic resonance imaging (MRI)-defined cortical depth and cyto-architectonically defined layers, the attainable resolution is sufficient to measure cortical layer–specific BOLD signals. This allows us for the first time to interrogate human brain circuits at unprecedented spatial resolution and distinguish information pathways in the human brain in line with functional neuroanatomy predictions, bridging the gap between animal and human neuroscience knowledge. Furthermore, UHF fMRI enables us to characterize how the human brain represents information across three (i.e., including depth), rather than two, dimensions of the cortical surface (Kuehn & Sereno 2018), offering a unique methodology to investigate interareal communication at a finer-grained scale than was previously possible in humans. Below, we review recent studies that use UHF fMRI across cortical depth to uncover information pathways involved in visual perception and cognition, shedding light on competing hypotheses and controversial findings.

3D Perception

Perceiving depth structure from binocular signals supports our ability to interact in our 3D environments (i.e., perceive and navigate 3D scenes, interact with 3D objects). The past decade has seen notable progress in identifying key nodes in the human visual cortex involved in stereoscopic processing. For example, human neuroimaging studies have revealed widespread responses to binocular signals in occipitoparietal regions (Bridge & Parker 2007, Welchman 2016), with the strongest modulation of brain activity by binocular signals found in areas V3A and V7 (Goncalves et al. 2015, Preston et al. 2008). However, the fine-scale computations that support depth perception in the human brain remain largely unknown. Work combining recent advances in laminar fMRI and multivoxel pattern analysis (MVPA), a method leveraging distributed patterns of activity to detect differences between conditions, demonstrates cortical depth-specific representations in area V3A; that is, higher MVPA accuracy (i.e., supporting discrimination of near versus far 3D planes) for correlated (i.e., stable stereoscopic perception) than anticorrelated (i.e., no consistent perception of 3D structure) stimuli was evident in the upper compared to deeper V3A layers (Ng et al. 2021). Furthermore, this study used UHF fMRI to interrogate the finer functional connectivity across brain areas (i.e., as measured by correlations of activity between brain areas) based on known anatomical models of connectivity across cortical layers. The results demonstrated that V3A is a key nexus for disparity processing that coordinates feedforward information to V7 and feedback signals to V1. By leveraging this finer-scale (layer-to-layer) information-based connectivity analysis, this study provides a new way to interrogate functional circuits using UHF fMRI, which was not previously possible using standard fMRI.

Perceptual Plasticity: Adaptation and Learning

Experience and training are known to mold the brain's organization and functions. In this section, we consider two forms of brain plasticity: (*a*) perceptual adaptation, which involves short-term changes in neural signals due to repeated exposure to the same stimulus, and (*b*) perceptual learning, which relates to longer-term training-induced plasticity. We demonstrate that UHF fMRI serves as a robust tool for uncovering the fine-scale mechanisms that support perceptual plasticity and adaptive behavior.

Perceptual adaptation is a form of short-term brain plasticity that is known to result in decreased brain responses due to repetitive sensory stimulation. Previous neurophysiological studies revealed adaptation at early stages of sensory processing. Recent work leveraged UHF fMRI to interrogate adaptation mechanisms at finer scale in the human brain (Zamboni et al. 2020). This study showed decreased activity for orientation adaptation (i.e., when gratings were presented at the same versus different orientations) across visual areas (from V1 to V4). Interestingly, stronger fMRI adaptation was observed in middle and superficial layers compared to deeper layers. Functional connectivity analyses revealed enhanced feedforward connectivity from V1 to extrastriate areas, suggesting local recurrent processing—predominantly in upper layers—with signals forwarded from early to higher visual areas. Furthermore, enhanced feedback connectivity was observed from the intraparietal sulcus (IPS) to V1, suggesting long-range feedback signals from the posterior parietal cortex that may relate to the expectation of familiar information. In line with the predictive coding theory, it is possible that these feedback expectation signals are compared to recurrent information in V1 superficial layers to support adaptive sensory processing.

Perceptual learning relates to our ability to optimize our perceptual judgements through training (Gilbert & Li 2012, Hooks & Chen 2020). Accumulating evidence suggests that experience and training change not only the developing but also the adult brain (Jia et al. 2020, 2021a). Efforts to understand how these experience-dependent changes are implemented in the adult brain

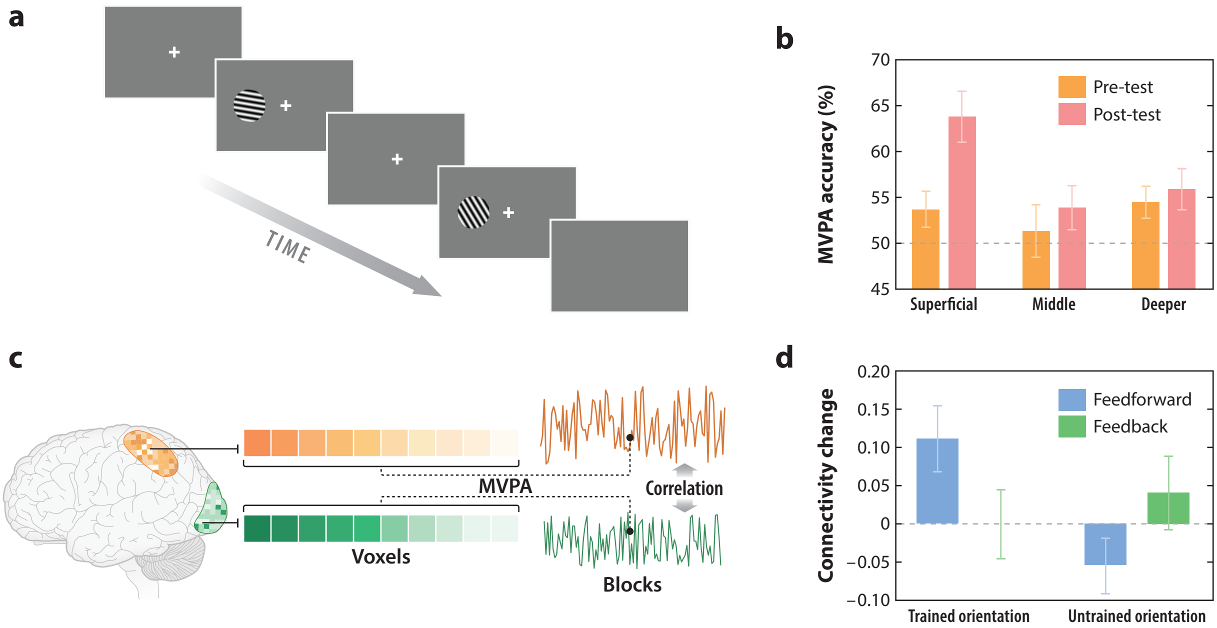

Figure 3

Ultra-high field functional magnetic resonance imaging across cortical depth reveals layer-specific, learning-dependent changes in V1. (*a*) An orientation discrimination task. Participants were asked to report whether the second grating was tilted clockwise or counterclockwise relative to the first one. (*b*) Enhanced multivoxel pattern analysis (MVPA) accuracy for the trained orientation after training is specific to the superficial V1 layers. (*c*) Schematic illustration of the MVPA-based connectivity analysis. (*d*) Learning-dependent functional connectivity increases between superficial V1 layers and middle IPS layers (feedforward connectivity; *blue bars*), rather than between deeper V1 and IPS layers (feedback connectivity; *green bars*), for the trained compared to the untrained orientation. Figure adapted with permission from Jia et al. (2020).

have led to a vigorous debate between differing accounts claiming that learning involves changes in sensory encoding versus top-down feedback. Standard fMRI cannot resolve this debate due to its limited spatial resolution. For example, activity changes in V1 after training observed by standard fMRI may reflect plastic changes in the LGN or V2 that are fed forward or backward to V1, respectively (Dorjee & Bowers 2012). A recent study combined UHF fMRI with a classic perceptual learning paradigm (training on orientation discrimination; **Figure 3*a***) to distinguish among these conflicting hypotheses (Jia et al. 2020). Interestingly, this work showed that neither of the dominant accounts of sensory plasticity (i.e., encoding versus feedback) explains the learning-dependent changes in brain activity. Instead, the results demonstrated the key role of recurrent processing in experience-dependent plasticity, showing that learning alters brain representations in superficial V1 layers rather than stimulus encoding in middle layers (**Figure 3*b***). Furthermore, functional connectivity analysis showed enhanced feedforward, rather than feedback, connectivity in occipitoparietal circuits (**Figure 3*d***).

These results are consistent with single-unit electrophysiology studies showing plastic changes in superficial V1 layers (Schoups et al. 2001). As horizontal connections across V1 columns are known to predominantly terminate in superficial layers (Douglas & Martin 2007, Gilbert & Wiesel 1983), these results provide support for recurrent processing within the visual cortex (Schwabe & Obermayer 2005, Self et al. 2013). It is possible that orientation-specific, learning-dependent changes in superficial V1 layers are due to iso-orientation inhibition (Malach et al. 1993), that is, suppression of neurons that are selective for the same orientation across columns. Iso-orientation inhibition is shown to be more pronounced in superficial layers and supports orientation tuning via horizontal connections between V1 columns (Douglas & Martin 2007, Gilbert & Wiesel 1983, Rockland & Pandya 1979, Shushruth et al. 2012).

Visual Attention

Selective attention is known to facilitate task performance by prioritizing processing of relevant information, yet the mechanisms underlying attention-related task improvement remain under debate. UHF fMRI affords the resolution to resolve conflicting findings across different species and studies employing different techniques. Specifically, previous work investigated whether attentional effects on contrast-response functions (CRFs) reflect additive or multiplicative computations. In contrast to neural signals measured by electrophysiological methods [electroencephalogram (EEG) or single-unit recording], which support multiplicative modulations of attention on CRFs (Di Russo et al. 2001, McAdams & Maunsell 1999, Reynolds et al. 2000), 3T fMRI studies have found attention-induced additive baseline shifts in the BOLD signal. These findings have been suggested to relate to potential fMRI artifacts, as the BOLD signal is aggregated across neurons that largely vary in their semisaturation points. To test this possibility, Liu et al. (2021) used ultra-high-resolution (0.3 mm in-plane) fMRI and found multiplicative effects of spatial attention in superficial and deep V1 layers, in contrast to the findings of additive effect measured with traditional gradient echo-echo planar imaging BOLD at lower spatial resolution. These findings resolved the long-standing discrepancies between attention effects measured using different techniques (fMRI versus electrophysiological) and are reconciled with the normalization models of attention that predict nonlinear modulations of CRFs (Reynolds & Heeger 2009). Combing UHF fMRI with appropriate pulse sequences affords strong potential to answer outstanding questions: For example, how do different types of attention (e.g., spatial- and feature-based attention) interact in layer-specific signals? How does selection history (a third modulatory factor proposed by recent theories of attention) modulate stimulus-evoked responses?

Visual Working Memory

Working memory refers to our ability to maintain and manipulate information for a short period of time. Despite extensive neuroimaging work, several questions related to the neural mechanisms of working memory remain open (D'Esposito & Postle 2015). A leading hypothesis posits the importance of persistent activity in the prefrontal cortex during information maintenance (Sreenivasan & D'Esposito 2019). This persistent activity reflects relevant properties associated with memory: (*a*) Neurons in the prefrontal cortex keep firing during the delay period, (*b*) the delay period activity disappears once it is no longer necessary to memorize information, (*c*) persistent activity is specific to the memorized features, and (*d*) persistent activity is not contaminated by motor preparation signals or attention. According to previous modeling work, similarly tuned pyramidal neurons from upper layers (i.e., layer III) serve as the source of glutamatergic excitatory recurrent connections that contribute to persistent activity (Goldman-Rakic 1995). To test this layer specificity, Finn et al. (2019) used UHF fMRI to measure activity in the dorsolateral prefrontal cortex (dLPFC) while participants performed a delayed response task. Unexpectedly, superficial layers in the dLPFC showed higher activity for manipulation of memorized information than for maintenance only; in contrast, activity in deeper layers increased during the response period (Finn et al. 2019). These results suggest that superficial layers of the dLPFC are involved in manipulation of working memory, while memorized information may be stored in other regions (prefrontal, parietal, or occipital), and the motor-related processes may be linked to the deeper layers of the dLPFC. Future work may expand coverage to parietal and sensory areas to interrogate interareal interactions during the perception, maintenance, and manipulation processes of working memory.

Furthermore, the sensory recruitment theory posits an important role for sensory cortices in holding mnemonic information, beyond frontoparietal networks (Harrison & Tong 2009). In particular, patterns of activity (i.e., MVPA) in the visual cortex were found to carry feature information in the absence of persistent activity (i.e., as revealed by univariate analysis), while persistent delay period activity was evident in prefrontal areas but without decodable feature information (Riggall & Postle 2012). Recently, the sensory recruitment theory has been challenged by studies showing that visual distraction during the working memory delay interferes with representations in early sensory cortex (Bettencourt & Xu 2015). A UHF fMRI study (Lawrence et al. 2018) examining the layer-specific representation of working memory was able to resolve these controversial findings by showing working memory–related activity in the agranular layers of V1, in contrast to sensory stimulus activity, which occurred across the entire cortical column. Thus, UHF fMRI reveals separate representations of bottom-up and top-down signals in the visual cortex, deepening our understanding of the cognitive processes that influence sensory processing (Iamshchinina et al. 2021).

USING ULTRA-HIGH FIELD FUNCTIONAL MAGNETIC RESONANCE IMAGING TO RESOLVE THE COLUMNAR ORGANIZATION AND INTRA-AREAL COMPUTATIONS IN THE HUMAN BRAIN

UHF fMRI is a useful tool not only for mapping processes across cortical depth, but also for measuring brain activity along the cortical surface, enabling columnar imaging. Columnar imaging can be used to (*a*) map the columnar organization and mesoscale connectome in the human brain and (*b*) advance our understanding of the computational mechanisms underlying cognition by measuring brain activity from the basic information preprocessing units (i.e., columns).

Resolving the Columnar Organization

UHF fMRI work has resolved cortical columns noninvasively in the human brain, including ODCs (Cheng et al. 2001, Menon et al. 1997, Yacoub et al. 2007), orientation columns in V1 (Sun et al. 2013, Yacoub et al. 2008), columnar-like stripes in the extrastriate cortex (Nasr et al. 2016, Tootell & Nasr 2017), motion directional columns in the human middle temporal area (hMT+) (Schneider et al. 2019, Zimmermann et al. 2011), and frequency preference columns in the primary auditory cortex (de Martino et al. 2015, Moerel et al. 2018). As cortical columns consist of neurons with similar neural tunings, UHF columnar imaging offers unprecedented opportunities to investigate fundamental aspects of neuronal computations.

Ocular dominance columns. In primate early visual cortex, geniculostriate projections to each eye are strictly segregated in layer 4C. Although neurons in the agranular layers show less preference to input from one eye than from the other, ocular dominance is consistently observed across cortical layers, resulting in ODCs. While ODCs are mainly resolved in cats and monkeys using histological stains, single-unit recording, and optical imaging, they have also been reconstructed in human postmortem brains stained with cytochrome oxidase (Adams & Horton 2009, Adams et al. 2007). ODCs are oriented orthogonally to the V1/V2 borders and approximately 1 mm in width (Adams et al. 2007), making them difficult to resolve noninvasively using standard fMRI. Nevertheless, recent advances in imaging techniques and sequence optimization allow us to measure brain activity with an in-plane resolution of 0.5 mm and identify columnar organization in the human cortex. Several studies have successfully mapped ODCs in the human brain (Cheng et al. 2001, Menon et al. 1997, Yacoub et al. 2007) by leveraging the high SNR afforded by UHF fMRI, carefully choosing a prolonged stimulation and differential mapping paradigm, precisely selecting participants and prescribing imaging slices, and meticulously excluding the signal from the large surface veins. These ODC maps were shown to replicate across scans and sessions and follow the classical properties of ODCs observed in monkeys and human postmortem brains, demonstrating that UHF fMRI can be used reliably to resolve the basic computational units of the human brain.

Orientation and motion direction columns. Mapping orientation columns in the human V1 is more challenging than mapping ODCs, as the width of the orientation columns (approximately 0.6–0.8 mm) is narrower than that of ODCs, which is especially a problem given that the nominal spatial resolution of UHF fMRI is lower than 0.5 mm and the point spread function is approximately 0.7 mm for spin echo BOLD (SE-BOLD) or cerebral blood volume and approximately 1.8 mm for gradient echo BOLD (GE-BOLD). However, using UHF SE-BOLD fMRI and the standard phase-encoding method (Engel et al. 1997, Sereno et al. 1995), Yacoub et al. (2008) managed to reveal orientation columns in the human visual cortex. Consistent with monkey studies, these orientation columns were shown to be organized in a pinwheel fashion. Further studies in the cat visual cortex found that functional orientation maps generated using GE-BOLD and SE-BOLD are correlated with each other and with the maps generated using optical imaging, providing evidence that orientation preference maps resolved by UHF fMRI reflect neural activity from orientation columns (Fukuda et al. 2006, Moon et al. 2007).

Outside the primary visual cortex, columnar organization has also been resolved in the hMT+. Using the zoomed 3D gradient and spin echo (GRASE) imaging sequence with submillimeter resolution (0.8 mm isotropic), Zimmermann et al. (2011) found smooth changes in the preference of motion-selective features that extend through cortical layers. The estimated column cycle is approximately 2–4 mm based on a topographic columnar simulation (Chaimow et al. 2011). This organization of axes-of-motion maps in the human middle temporal area has been recently reproduced using the blood-volume-sensitive vascular space occupancy (VASO) sequence (Pizzuti et al. 2023).

Columnar stripes in the extrastriate cortex. Beyond the primary visual cortex, in extrastriate areas, different visual features are processed in segregated pathways. For example, color perception is mainly preprocessed in the outer four LGN layers (i.e., parvocellular layers, known as the P pathway), whereas the inner two magnocellular layers are involved in motion and depth perception (the M pathway). These two separate streams extend to the primary visual cortex, where the M pathway projects to layer 4Cα, and the P pathway projects to layer 4Cβ. UHF fMRI has successfully resolved two columnar stripes in V2 and V3 (thin versus thick stripes). These stripes radiate perpendicularly from the V1–V2 border, consistent with monkey neurophysiology studies. Thin stripes show larger response to color stimuli, whereas thick stripes are mainly driven by depth information (Nasr et al. 2016, Tootell & Nasr 2017).

Using Columnar Imaging to Interrogate Computational Mechanisms

Columnar imaging can serve as a powerful tool to understand how brain functions are constrained by anatomical organization. For example, using UHF fMRI to resolve orientation dominance columns in human V1 revealed that more voxels prefer cardinal orientations, consistent with evidence for higher perceptual sensitivity for cardinal than for oblique orientations. Furthermore, this over-representation of cardinal orientations is mainly found near horizontal and vertical-meridian representations that may serve as the neural basis of radial bias (Sun et al. 2013), that is, a preference for orientations parallel to the line connecting a given position with the fixation.

Furthermore, columnar imaging allows us to interrogate brain activity at the neuronal population level. Although MVPA is commonly used in fMRI studies to resolve information content across large-scale neural populations, interpreting the computational processes reflected by the decoding accuracy derived from the MVPA remains difficult (Haynes & Rees 2005, Kamitani & Tong 2005). The forward encoding model (FEM), also called the inverted encoding model (IEM), offers the promise of revealing the populational- or channel-level responses (Brouwer & Heeger 2009, 2011). Encoding approaches estimate the weight of different neural populations per voxel by assuming that the activity of each voxel is the linear summation of different neural populations and modeling the shape of the neural tuning of neural populations to different visual stimuli (e.g., orientations). A combination of the IEM with fMRI or EEG has been used to examine how cross-orientation suppression (Brouwer & Heeger 2011), perceptual learning (Chen et al. 2015), visual attention (Ester et al. 2016, Sprague & Serences 2013), and working memory (Ester et al. 2015, 2018; Sprague et al. 2016) affect the activity of neural populations, providing a link between neurophysiology and human neural imaging studies. However, whether the output channel response reflects the actual neural population activity is still debated, as the SNR in the fMRI data may affect the model's neural tuning estimation (Gardner & Liu 2019, Liu et al. 2018). In contrast, columnar imaging provides a more direct way to measure the brain activity at the neural population level, as it measures brain activity from a population of neurons preferring similar stimuli in a column.

For example, Schneider et al. (2019) were able to predict from activity profiles in axis-of-motion columns in hMT+ which of two possible interpretations of ambiguous apparent motion stimuli (horizontal or vertical motion) was consciously perceived. Horizontal and vertical axis-of-motion columns in area hMT+ were mapped prior to the main experiment using physical horizontal and vertical motion stimuli. When the constant two-frame ambiguous apparent motion stimulus of the main experiment was interpreted as horizontal (vertical) motion, the activity in the localized horizontal (vertical) axis-of-motion columns increased, while the activity in the localized vertical (horizontal) axis-of-motion columns decreased (**Figure 4**). These results demonstrate that content-specific neural correlates of perception can now be studied in the human brain at the level of differential activity patterns in neighboring functionally defined cortical columns.

SUBCORTICAL IMAGING

In addition to measurements across cortical depth and cortical columns, UHF fMRI affords measures of brain activity in small subcortical areas. For example, combining UHF fMRI with a figure-ground segmentation paradigm, Poltoratski et al. (2019) showed an attention-independent figure enhancement of neural activity in V1 and the LGN that holds when the figure and background stimuli are presented to different eyes. These results suggest that, as information from different eyes starts to integrate in V1, contextual feedback goes from V1 to the LGN. Furthermore, the human LGN can be segmented into six different layers. Layers 1, 4, and 6 receive input from the contralateral eye, whereas layers 2, 3, and 5 receive input from the ipsilateral eye. Color and motion information are also separately represented in different layers (P versus M pathways). Leveraging UHF fMRI, a recent study resolved these eye-specific and P- versus M-specific brain signals in different LGN layers, providing the possibility of investigating neural computations in the LGN (Qian et al. 2020).

RESOLVING THE MESOSCALE CONNECTOME

A key application of UHF MRI is to uncover the directional brain connectome (i.e., feedforward versus feedback pathways). In the past decades, brain networks have been intensively mapped at the microscale level using single-unit recordings and at the macroscale level using resting-state fMRI. UHF fMRI provides a new tool for uncovering the mesoscale connectome and bridging

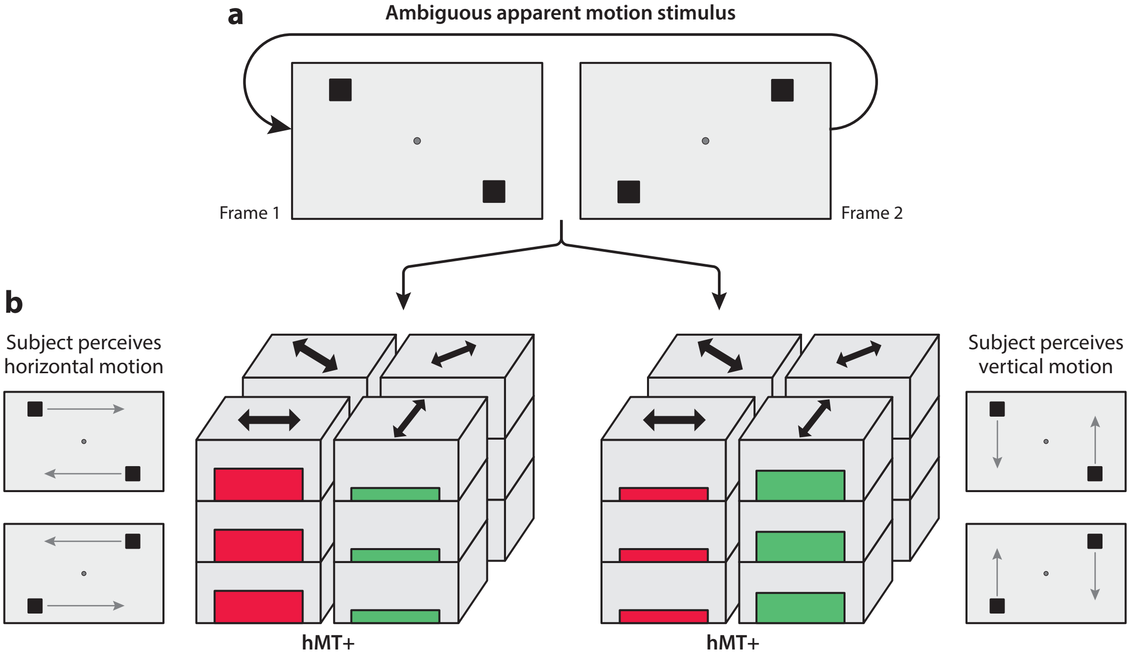

Figure 4

Columnar-level content-specific neural correlates of motion perception (Schneider et al. 2019). (*a*) Ambiguous motion stimulus. Two frames were presented, alternating every 500 ms; each frame contained two nonmoving (static) squares. (*b*) Result. The ambiguous motion stimulus is perceived as either horizontal or vertical motion switching approximately every 10 s (perceived motion direction indicated by arrows that are not shown to participants). The perceived interpretation (horizontal or vertical motion) was reflected in differential activity in previously localized horizontal and vertical axis-of-motion columns in the hMT+ (activity in horizontal and vertical motion columns indicated by red and green activity levels, respectively). Abbreviation: hMT+, human middle temporal area.

the gap between animal and human studies across scales. In particular, using standard resting-state fMRI, past research mapped functional connectivity across the brain based on correlations of spontaneous activity between functionally related brain areas that predict cognitive performance. Subsequent work capitalized on advanced computational approaches (e.g., graph theory, small-world networks, and deep neural networks) to identify neural biomarkers of neurocognitive disorders (including Alzheimer's disease, major depressive disorder, schizophrenia, and autism spectrum disorders). Using UHF fMRI to measure neural activity at submillimeter resolution allows us to build a layer-dependent functional connection map (i.e., 3D directional connectome). For example, Tootell & Nasr (2017) used UHF resting-state connectivity analysis and found that voxels from two anatomically and functionally separated pathways (M versus P) in the human brain show lower coherence in BOLD activity than voxels from the same pathway and that this separation extends throughout the visual cortex. Mapping this directional mesoscale connectome has the potential to advance our understanding of information flow by identifying the key nodes and interactions underlying cognitive functions and their impairments in brain and mental health disorders.

Furthermore, a series of brain perturbation techniques, such as transcranial magnetic stimulation, transcranial focused ultrasound stimulation, and deep brain stimulation, have been combined with fMRI to map the brain connectome (Klink et al. 2021). Interestingly, a newly developed pulsed near infrared neural stimulation (INS) method has been shown to induce focal neuron activities in a single column through a thermal mechanism (Cayce et al. 2014) and reveal the mesoscale connectome both within and between areas. In particular, stimulating a single ODC in V1 selectively increases the activities of nearby same-eye columns, whereas stimulation of single orientation domains induces enhanced visual activities of similar orientation domains and decreased visual activities of nonsimilar orientation domains (Chernov et al. 2018). Moreover, INS in cat area 17/18 also induced visual responses from subcortical areas (e.g., the LGN, pulvinar) to the extrastriate cortex (Xu et al. 2019) following anatomical connectivity.

KEY CHALLENGES IN ULTRA-HIGH FIELD FUNCTIONAL MAGNETIC RESONANCE IMAGING

Draining Vein Effects in Blood-Oxygen-Level-Dependent Functional Magnetic Resonance Imaging

Mapping of brain function across cortical layers and cortical columns has been conducted mainly using BOLD fMRI because of its high sensitivity in detecting brain activation (as compared to alternative fMRI techniques; see below) and because of its widespread availability. BOLD fMRI suffers, however, from major limitations when it is aimed at a precise localization of neuronal activation. A major reason for this is that conventional 2D GE-BOLD measurements are confounded by signals originating from the large draining veins, causing signal dephasing. These venous effects may appear as activation that is displaced from the original site of neural activity by as much as 4 mm (Turner 2002). Since draining veins are predominantly located at the pial surface, and venous blood ascends from deep to superficial layers, this results in the common observation of increasing activity from deep to superficial layers in laminar GE-BOLD fMRI (Polimeni et al. 2010). Exploiting knowledge of the vascular system along cortical depth (**Figure 5**), one can mitigate venous effects by measuring BOLD responses from the microvasculature (capillaries and small venules) while avoiding responses from the macrovasculature (e.g., Ugurbil 2016). One way to achieve this is to use alternative fMRI techniques that are less sensitive to the macrovasculature (see the next section), but these approaches come with their own limitations, such as reduced sensitivity. Many researchers thus use GE-BOLD fMRI and have proposed other means to mitigate venous-related signals from the fMRI data. One simple approach is to restrict analysis to cortical depths below the pial surface, often in combination with a surface-based approach (Kemper et al. 2018, Polimeni et al. 2018). This approach can be further improved by identifying draining veins in superficial layers by their darker intensity signature and excluding such voxels from further analysis (e.g., Muckli et al. 2015). Kay et al. (2020) recently proposed a fully automatic method to mitigate venous effects by exploiting the observation (Siero et al. 2011) that BOLD time course amplitude, delay, and width increase from deep to superficial cortical depths. With a series of analysis steps, this temporal decomposition through manifold fitting (TDM) method consistently removes venous effects while maintaining a reasonable level of sensitivity.

Increasing Neuronal Specificity Using Non-BOLD Functional Magnetic Resonance Imaging

To mitigate the limitations of GE-BOLD fMRI, an extensive range of alternative fMRI techniques have been proposed, such as 3D GRASE (Oshio & Feinberg 1991), arterial spin labeling (Ivanov et al. 2017), and steady-state free precession (Goa et al. 2014), and used for laminar and columnar fMRI (Qian et al. 2020, Zimmermann et al. 2011). In recent years, one of the fastest growing alternative approaches for layer-based fMRI utilizes slice-saturation slab-inversion (SS-SI) VASO (Huber et al. 2014). The VASO contrast exploits the difference between the longitudinal relaxation times (T1) of tissue and blood (Lu et al. 2003). Despite its lower sensitivity with respect to

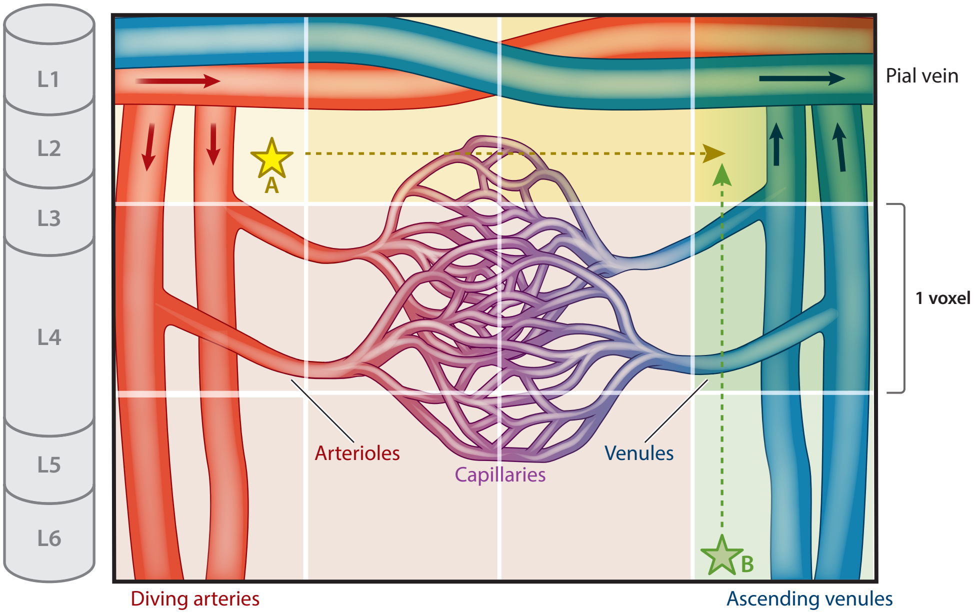

Figure 5

Ultra-high field functional magnetic resonance imaging (fMRI) limitations: partial volume and draining vein effects. In partial volume effects, voxels are large and sample activity from multiple layers to varying degrees; in the figure, the voxel grid is aligned with the orientation of the layers, which is not the case in real measurements. In draining vein effects, the measured signal of the upper-right voxel is confounded by neural activity at locations A and B due to the draining veins located at the pial surface and the ascending venules running perpendicular to the cortical surface, respectively.

GE-BOLD fMRI, many recent laminar fMRI studies have demonstrated its higher neuronal specificity (e.g., Huber et al. 2021b). Instead of a signal increase from deep to superficial layers, as observed in GE-BOLD fMRI, the VASO signal stays rather constant across depth. When providing visual stimuli, for example, the laminar profile of active regions in the primary visual cortex shows a peak in the middle layers and weaker activity in both superficial and deep layers, as predicted by the canonical microcircuit of the cortex (**Figure 2**).

While alternative fMRI techniques such as VASO, 3D GRASE, and spin-echo acquisition mitigate venous effects and generally provide more neuronally specific signals, they usually require longer volume acquisition times and provide lower contrast-to-noise ratios compared to GE-BOLD fMRI. As a consequence, one often is forced to reduce spatial coverage and to substantially increase the amount of data collected per experimental condition to obtain sufficient measurement sensitivity.

Data Preprocessing: Distortion, Motion Correction, Smoothing

Laminar and columnar fMRI require optimized data preprocessing, since even small issues with respect to head motion, image distortion, and functional-anatomical coregistration may render submillimeter UHF data useless. This high vulnerability to artifacts is related, on the one hand, to the employed small voxel size and small imaging slabs and, on the other hand, to magnetic field inhomogeneities that lead to stronger geometric image distortions and intensity inhomogeneities over the brain than do conventional field strengths.

Spatial smoothing. Since the purpose of mesoscale fMRI is the resolution of fine-grained spatial details, spatial smoothing of the data is usually not recommended. While smoothing reduces noise, the typically employed isotropic Gaussian 3D kernel blurs signals across neighboring segmented boundaries such as layer compartments. For smoothing to be beneficial for laminar and columnar analyses, more flexible nonisotropic smoothing kernels are needed that extend more tangentially along the cortex for laminar smoothing or more vertically for columnar smoothing. Such spatially informed smoothing approaches (Kiebel et al. 2000) have been applied in laminar fMRI to smooth tangentially along the extension of the cortex restricted to layers as defined by specific laminar depth ranges (Blazejewska et al. 2019, Huber et al. 2021a).

Motion correction. In UHF imaging, the small (submillimeter) voxel size and typically small imaging slabs put special demands on motion correction. Even motion on the order of a millimeter is considered high in this context, and more stringent data exclusion criteria are used compared to whole-brain scans with a standard voxel size (e.g., 2 mm at 3 Tesla). Minimizing head motion should start in the scanner. Besides instructions not to move, bite bars or simple tactile feedback such as a strip of medical tape applied from one side of the head coil via the participant's forehead to the other side may substantially reduce head motion (Krause et al. 2019). Another approach to mitigating head motion effects is to detect and correct motion online during scanning using prospective motion correction. This technique detects motion parameters during acquisition using recorded images (Thesen et al. 2000) or external optical tracking (Speck et al. 2006) and then updates pulse sequence parameters in such a way that the imaging slab follows the moving head of the participant (MacLaren et al. 2012). While prospective motion correction techniques are very useful, errors during motion detection may lead to wrong adjustments that, in the worst case, might even introduce motion artifacts. Such techniques thus need to be carefully evaluated for UHF imaging and used with care.

At ultra-high fields, it is also advisable to instruct participants not only to avoid head movements but also to keep their limbs still for the duration of the scan, since limb movements may introduce small, unintended movements of the head. In addition, limb movements might modify the magnetic field near the head, increasing artifacts such as image distortions.

Even when following the advice above, small head movements will be present in the data and should be corrected using offline motion correction routines that aim to align each functional volume to a reference. Unfortunately, standard motion correction routines do not work very well in the case of small imaging slabs and data with low tissue (white or gray matter) contrast. Furthermore, using small slabs bears the risk that the targeted cortical region might partially move out of the field of view, which cannot be recovered by motion correction postprocessing. Another point to consider concerns across-run motion correction: The common practice at conventional magnetic field strengths to allow participants to relax (and thus probably move) between runs should be avoided in UHF imaging, especially when using small imaging slabs.

Image distortions and functional–anatomical coregistration. The accurate alignment of functional data with anatomical reference images is crucial for the analysis of laminar and columnar fMRI studies. Grey matter tissue and layer compartments are usually segmented on anatomical images, since they provide better gray and white matter contrast than functional volumes. In the case where coregistration is not precise enough, gray matter voxels in specific layer compartments defined in the anatomical image may sample wrong layers, or even cerebrospinal fluid or white matter voxels, in the functional data. To mitigate this issue, functional data should be corrected for spatial distortions using field maps or opposite phase-encoded images when using EPI. To further limit misalignments, it is advisable to limit coregistration to the target region by using spatially restricted (mask-based) alignment. For example, in the case of laminar analysis of motion-selective areas, alignment should be optimized for a posterior location covering the (functionally localized) region around V3A and MT+ (V5), while remote regions in the slices covering, e.g., the frontal cortex can be ignored.

An ingenious approach eliminates the need to undistort the fMRI images by acquiring anatomical data with high gray and white matter tissue contrast that matches the distortion of the functional images (Kashyap et al. 2018). In the case in which the functional acquisition technique used retains sufficient gray/white matter contrast, one can even go a step further and use the functional data themselves to perform gray matter segmentation and laminar parcellation (e.g., Fracasso et al. 2016).

Partial Volume Effect

Although the voxel size in UHF fMRI is usually in the submillimeter range, it is still large with respect to the targeted mesoscopic regime of cortical layers and cortical columns, and therefore, partial volume effects are common. Partial volume effects can be corrected at the subvoxel level: Provided that an accurate measure of the laminar composition of each voxel exists, the contribution of layers generating the observed fMRI signals can be estimated. To predict the partial volume fraction of a specific layer in a voxel, the borders of layers need to be estimated as accurately as possible along the folded cortex using techniques such as the equivolume layer sampling scheme (Kemper et al. 2018, Waehnert et al. 2014). Given knowledge of how (neighboring) layers contribute to each voxel, a spatial general linear model (GLM) (van Mourik et al. 2019) can be fitted to the measured voxel activity values (dependent variable). For each layer, a separate predictor is defined in the design matrix containing the layer-specific partial volume measures for each voxel. The beta weights fitted by the spatial GLM correspond to the true mean activity of the respective layers, which are assumed to be constant across the considered region of interest. The activity estimates for all layers provide a partial volume-corrected laminar profile for the investigated activated brain region. Note, however, that partial volume correction requires a sufficiently large number of voxels to enable (stable) estimation of laminar-specific contributions. It is, thus, not applicable if pooling across a larger cortical extent is not desirable, for example, when analyzing depth profiles along small regions such as individual functional columns. Furthermore, partial volume estimates themselves can be inaccurate: Any error in the estimation of the positions of the layers with respect to the voxels will cause errors in the resulting laminar profiles, since the spatial GLM will use suboptimal predictors in the design matrix. To limit such errors, an optimal functional-to-anatomical alignment (see the previous section) is needed, as well as an accurate-as-possible estimation of laminar parcellation.

FUTURE DIRECTIONS

Further Enhancement in Signal-to-Noise Ratio

Despite its enhanced SNR compared to standard 3T fMRI, UHF fMRI is still limited by different sources of noise (e.g., thermal noise, cardiac and respiratory oscillation). Developing new data acquisition and analysis pipelines that can reduce the noise levels will further expand the research and clinical capability of UHF fMRI. Vizioli et al. (2021) developed a noise reduction with distribution corrected principal component analysis (PCA) method that targets the zero-mean Gaussian-distributed thermal noise, improving the temporal SNR and the detection power of UHF fMRI by 300–500%. Similarly, Kay et al. (2013) used PCA to identify the noise regressors and entered these regressors into GLMdenoise, improving the SNR of the data and the cross-validation accuracy of GLM estimates. In addition to PCA, independent component analysis and deep neural networks (Yang et al. 2020) have also been developed for 3T fMRI. Future studies may further develop and implement these denoising methods to improve the SNR and statistical power of UHF fMRI.

Further Enhancement in Temporal Resolution

In this review, we mainly focus on UHF fMRI's improved spatial resolution; however, it also allows acquisition of functional images with subsecond temporal resolution to enhance the statistical gains and uncover the neural dynamics underlying cognition (Dowdle et al. 2021). For example, Toi et al. (2022) developed a two-dimensional fast line-scan approach (DIANA) for UHF fMRI (9.4T) that directly images neural activity, rather than BOLD, on the order of milliseconds while retaining high spatial resolution. Application of DIANA provides a unique opportunity to investigate neural dynamics at high spatial resolution in the human brain. Further work is needed to optimize the hardware (e.g., parallel imaging techniques) and acquisition sequences to improve coverage for application to neuroscience and clinical studies.

Finally, combining UHF fMRI with EEG and magnetoencephalography (MEG) allows brain imaging at both high spatial and high temporal resolution. Different EEG and MEG oscillatory activity has been shown to be related to feedforward versus feedback pathways. In particular, alpha and beta band activity has been shown to mainly reflect feedback information, whereas gamma band activity mainly reflects feedforward signals. In line with this finding, simultaneous EEG-UHF fMRI revealed positive correlation between gamma band EEG activity and BOLD responses in the superficial layers and negative correlation between beta band EEG activity and BOLD responses in the deeper layers (Scheeringa & Fries 2019, Scheeringa et al. 2016). Future studies may use simultaneous EEG-UHF fMRI to link the oscillation activity to the cortical laminae and to interrogate interareal communications in the human brain.

Application of Laminar and Columnar Imaging Beyond Sensory Areas

In the past decade, UHF fMRI has been mainly used in the sensory cortex areas, including the LGN (Qian et al. 2020), V1 (Jia et al. 2020, Kok et al. 2016, Lawrence et al. 2019, Muckli et al. 2015), A1 (de Martino et al. 2015), and S1 (Yu et al. 2019). However, the laminar organization of other cortices is less understood (but see Finn et al. 2019). Further studies are needed to uncover the distinct functions of different cortical layers in the parietal cortex (PPC) and prefrontal cortex (PFC). Similarly, using columnar imaging to resolve the columnar organization has also been restricted to the sensory cortex, despite previous neurophysiological evidence that neurons preferring similar stimuli in the PFC and PPC are also grouped together (Masse et al. 2017). Whether a columnar organization exists in other cortices and the functional role of these columns need to be further investigated.

SUMMARY

UHF fMRI provides a robust mesoscopic (i.e., submillimeter resolution) tool that allows us to probe laminar and columnar circuits, discern feedforward and feedback pathways, and map small subcortical areas in the human brain. Although there are several challenges related to data acquisition and processing, application of UHF fMRI will deepen our understanding of the fine-scale computations and interareal communication that support visual cognition, bridging the gap between animal and human studies across scales.

SUMMARY POINTS

1. Ultra-high field (UHF) laminar functional magnetic resonance imaging (fMRI) affords the submillimeter resolution necessary to distinguish different pathways (feedforward versus feedback) in the human brain. This advanced imaging technique enables us to characterize how the human brain represents information in three dimensions, offering a unique opportunity to investigate directional interareal communication at a finer scale than was previously possible in the human brain.
2. UHF columnar fMRI allows us to map the columnar organization and mesoscale connectome in the human brain, advancing our understanding of the computational mechanisms underlying cognition by measuring brain activity at the level of the basic information preprocessing units (i.e., columns) in the human brain.
3. UHF subcortical fMRI allows us to map small subcortical areas and their connectivity to cortical areas, providing a high-resolution map of information processing in support of sensory and cognitive functions.

FUTURE ISSUES

1. Developing new imaging sequences with high temporal resolution (e.g., DIANA) may provide a unique opportunity to understand the neural activity during cognition.
2. New data acquisition and preprocessing methods (e.g., using deep neural networks) are needed to enhance the resolution and signal-to-noise ratio of UHF fMRI.
3. Laminar circuits and columnar organization need to be resolved beyond sensory areas to uncover the distinct functions of different cortical layers and columns across whole-brain networks and map the human brain connectome at finer scale.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

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Errata

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